Simulation Modeling of Zoonotic Diseases between Swine and Human Populations for Informing Policy Decisions

By

Sithar Dorjee

A Thesis
Submitted to the Graduate Faculty
in Partial Fulfillment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

Department of Health Management
Faculty of Veterinary Medicine
University of Prince Edward Island

CONDITION OF USE

The author has agreed that the Library, University of Prince Edward Island, may make this thesis freely available for inspection. Moreover, the author has agreed that permission for extensive copying of this thesis for scholarly purposes may be granted by the professor or professors who supervised the thesis work recorded herein or, in their absence, by the Chair of the Department or the Dean of the Faculty in which the thesis work was done. It is understood that due recognition will be given to the author of this thesis and to the University of Prince Edward Island in any use of the material in this thesis. Copying or publication or any other use of the thesis for financial gain without approval by the University of Prince Edward Island and the author's written permission is prohibited.

Requests for permission to copy or to make any other use of material in this thesis in whole or in part should be addressed to:

Chair of the Department of Health Management

Faculty of Veterinary Medicine

University of Prince Edward Island

Charlottetown, PE

Canada CIE 4P3

PERMISSION TO USE POSTGRADUATE THESIS

Title of thesis: Simulation Modeling of Zoonotic Diseases between Swine and Human Populations for Informing Policy Decisions

Name of Author: Sithar Dorjee
Department: Health Management

Degree: Doctor of Philosophy Year: 2013

In presenting this thesis in partial fulfillment of the requirements for a postgraduate degree from the University of Prince Edward Island, I agree that the Libraries of this University may make it freely available for inspection. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the professor or professors who supervised my thesis work, or, in their absence, by the Chairman of the Department or the Dean of the Faculty in which my thesis work was done. It is understood any copying or publication or use of this thesis or parts thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of Prince Edward Island in any scholarly use which may be made of any material in my thesis.

Signature:

Address:
Department of Health Management
Faculty of Veterinary Medicine
University of Prince Edward Island
550 University Avenue
Charlottetown, PE C1A 4P3
CANADA.

Date: December 18, 2013

University of Prince Edward Island

Faculty of Veterinary Medicine

Charlottetown

CERTIFICATION OF THESIS WORK

We, the undersigned, certify that Sithar Dorjee, a candidate for the degree of Doctor of Philosophy, has presented his thesis with the following title: **Simulation Modeling of Zoonotic Diseases between Swine and Human Populations for Informing Policy Decisions** and that the thesis is acceptable in form and content, and that a satisfactory knowledge of the field covered by the thesis was demonstrated by the candidate through an oral examination held on December 18, 2013.

Examiners

Dr. Elizabeth Spangler - Chair _____

Dr. Rob Deardon - External _____

Dr. Javier Sanchez _____

Dr. Dan Hurnik _____

Dr. María Forzán _____

Date: December 18, 2013

Abstract

Approximately 60% of human pathogens and emerging infectious diseases are zoonotic. Simulation models are increasingly being used to investigate the spread of diseases, evaluate intervention strategies and guide the decisions of policy makers. In this thesis a systematic review of modeling methods and approaches used for zoonotic influenza in animals and humans was conducted, and knowledge gaps were identified. Furthermore, the disease spread and intervention parameters used in these studies were summarized for ready reference in future work.

Building on this review work, the research presented in this thesis evaluated the effects of transmissibility of the pandemic H1N1 2009 (pH1N1) virus at the swine-human interface and the control strategies against its spread in swine and human populations as a case study for zoonotic disease modeling. The feasibility of North American Animal Disease Spread Model (NAADSM) for modeling directly transmitted zoonoses was also assessed. Population data based on swine herds and households (categorized as rural households with or without swine workers, and urban households without swine workers) of a county in Ontario, Canada was used. The swine workers served as a bridging population for the spread of the virus between swine herds and households. Scenarios based on the combinations of the transmissibility of the virus (low (L), medium (M), and high (H)) from swine-to-human and human-to-swine (LL, ML, HL, MM, HM, LL), and targeted vaccination of swine worker households (0% to 60%) were evaluated. The results showed that lowering the influenza transmissibility at the interface to low level and providing higher vaccine coverage (60%) had significant

beneficial effects on all outcome measures. However, these measures had little or negligible impact on the total number of rural and urban households infected. A set of models evaluating the combination of control strategies indicated that a moderate speed of the detection (within 5 to 10 days of the first infection), combined with the quarantine of detected units alone, contained the outbreak within the swine population in most simulations. However, a zone-based quarantine strategy was more effective when the detection was delayed until around three weeks after initial infection. Ring vaccination had no added beneficial effect. This work suggested that NAADSM can be used for modeling the directly transmitted zoonotic diseases under similar simplifying assumptions adopted in these studies. However, this needs to be evaluated further with more accurate parameters and influenza outbreak data.

To fill in some of the gaps identified in the review study, network analyses of swine shipments among farms, and between farms and abattoirs were conducted. This provided network metrics and parameters necessary for disease modeling and risk-based disease management in swine in Ontario for the first time. Finally, agent-based network models assessing the spread and control of pH1N1 in swine established the importance of explicitly incorporating appropriate contact network structures into such models to increase their validity. It also demonstrated the benefits of targeted control strategies against highly connected farms. In conclusion, the modeling tools developed in this thesis can assist decision makers in preparedness and response of outbreaks of infectious diseases as more information become available for the parameterization of models.

Acknowledgements

I remain grateful to the Atlantic Veterinary College, the Canadian Food Inspection Agency, and Animal Health Strategic Investment project of OMAFRA (Ontario Ministry of Agriculture and Rural Affairs) for providing the stipend and research funding supports. This has not only allowed me to pursue my PhD, but also to experience the culture, beauty and hospitality of this small beautiful Island. I am also grateful to the management of the Bhutan Agriculture and Food Regulatory Authority (BAFRA), Ministry of Agriculture and Forests, Royal Government of Bhutan for allowing me to pursue my PhD.

I feel privileged to be associated with the Centre for Veterinary Epidemiological Research (CVER), one of the premier institutes for veterinary epidemiology training and research in the world. I owe my profound gratitude to Dr. Javier Sanchez, my principal supervisor for his excellent mentorship and support provided throughout the journey of this PhD. He has enabled me to learn several advanced epidemiological and statistical tools, and truly broadened my skills in these areas. He and his family also extended a great help and support to my family at the personal level. For this we remain very grateful to you and your family!

I am equally indebted to Dr. Crawford Revie (my co-supervisor), Dr. Bruce McNab from OMAFRA, and Dr. Zvonimir Poljak from the Ontario Veterinary College, Guelph for their excellent guidance and supports, and providing numerous valuable ideas and suggestions during the implementation of the research. Dr. McNab and Dr. Poljak have provided great help during the initial phase of the implementation of this project and extended generous hospitality during my stay in Guelph. My appreciation and sincere thanks are also due to Dr. J.T McClure and Dr. María Forzán (members of my supervisory committee) for providing valuable inputs and contributions to this project. Had it not been for all your great support and guidance I would have not accomplished this PhD.

Professor Ian Dohoo was instrumental in facilitating my journey to AVC to pursue my PhD. He and his wife also provided my family a great support and hospitality during our stay here. For this I remain very grateful to him and his wife. I really appreciate Prof. Dohoo's vision to support and train young epidemiologists, particularly from the developing countries, and admire his excellent teaching skills. This is what inspires and motivates me to work harder and learn more!

I would also like to thank Dr. Henrik Stryhn for providing advice on some of the statistical analyses of my studies. I also thank other CVER faculty staff for their

professional and personal interactions that enhanced my learning skills. Special thanks are also due to Dr. Jeffrey Wichtel, Associate Dean of Graduate Studies and Research, Leanne Newson, Rosemary McIver, Barb Curley, and Darlene Wakelin for their administrative supports, and Erica Stanley from the International Student's Office for her numerous help and support during out stay here.

I would also like to thank all the past and present postgraduate colleagues: Alejandro Ceballos, Tim Burnley, Raphael Vanderstichel, Fernanda Dorea, Krishna Thakur, Thitiwan Patanasatienkul, Jia Beibei, Julian Reyes Velez, Gabriel Arriagada, Omid Nekouei, Ketan Dulal, Colleen Walton, Maya Groner Groner (postdoctoral fellow) and others for sharing their experiences, interactive discussions, friendship, and making my stay here enjoyable and memorable one. I owe special thanks to Thitiwan, Krishna and his wife Nitu Jha, Beibei and Jenny Yu for giving company to me and my family, and looking after my kids on few occasions.

Last but not the least, the supports and encouragement received from all my relatives at home are also gratefully acknowledged. I would like to thank my wife Kinzang Lhamo and three kids, Jambay Lhamo, Sonam Jurmin and Kezang Choden for their love and encouragement, and bearing with me during this whole process. I also dedicate this small piece of work to my dearest mother Rinchenmo and sister Yeshi Lhamo for all the love, care and sacrifices made in supporting my education.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ABM	Agent-based model
ABNM	Agent-based network model
AFT	Accelerated failure-time
AIAO	All-in all-out
AIC	Akaike Information Criterion
ANOVA	Analysis of variance
CAFO	Confined animal feeding operations
CDC	Centers for Disease Control and Prevention
CHeMM	Compartmental heterogeneous mixing models
CHoMM	Compartmental homogeneous mixing models
CI	Confidence interval
CSF	Classical swine fever
DE	Differential equations
FMD	Foot-and-mouth disease
GLM	Generalized linear model
HA	Hemagglutinin
HIV	Human Immunodeficiency virus
HH	High animal to human – High human to animal
HL	High animal to human – Low human to animal
HM	High animal to human – Medium human to animal
HPAI	Highly pathogenic avian influenza
IBM	Individual-based model
ID	Identity number
IIC	Incoming infection chain
KS	Kolmogorov-Smirnov
KW	Kruskal-Wallis
LL	Low animal to human – Low human to animal
MetM	Metapopulation models
ML	Medium animal to human – Low human to animal

MM	Medium animal to human – Medium human to animal
NA	Neuraminidase
NAADSM	North American Animal Disease Spread Model
NetM	Network models
OIE	Office International des Epizooties
OIC	Outgoing infection chain
pH1N1	Pandemic H1N1 2009
PIPM	Pandemic Influenza Policy Model (PIPM)
PRRS	Porcine respiratory and reproductive syndrome
PUs	Processing units
RH	Rural non-swine worker households
RN	Random network
R_0	Basic reproductive ratio
SARS	Severe acute respiratory syndrome
SDM	System dynamic model
SEARUMS	Studying the Epidemiology of Avian Influenza Rapidly Using Modeling and Simulation
SEIR	Susceptible - Exposed - Infectious - Recovered
SFN	Scale-free network
SIR	Susceptible - Infectious - Recovered
SH	Swine herds
SWH	Swine worker households
SWN	Small-world network
RePAST	Recursive Porous Agent Simulation Toolkit
UH	Urban non-swine worker households
WHO	World Health Organization

Chapter 1
Introduction and Objectives

Approximately 58% of the human pathogens and 60% of emerging infectious diseases are zoonotic diseases (Woolhouse and Gowtage-Sequeria, 2005, Jones et al., 2008). Furthermore, the incidence of zoonotic disease continues to increase and is causing significant impact on global health and economies (Jones et al., 2008). The main reasons for the increasing incidence of zoonoses include: population growth and climate change, the intensification of animal production systems, increased interaction between people, domestic and wild animals, and globalization which leads to increasing international movements of people, animals and food (Kuiken et al., 2006, Jones et al., 2008, Lloyd-Smith et al., 2009a, Woolhouse, 2011). These factors are decreasing the extent of geographical, environmental, or behavioral barriers that limit transmission of pathogens between different species of animals, and between animals and humans. In addition, they facilitate the evolution of pathogens and their adaptability in new host species (Woolhouse and Gowtage-Sequeria, 2005, Kuiken et al., 2006). The infectious nature and multihost ecology of zoonoses result in a complex non-linear transmission dynamics within or between different species of populations that necessitates new approaches and analytical tools for understanding the patterns of disease spread and the development of effective control policies. Mathematical and computer simulation modeling have been identified as one of the important tools for these purposes and are becoming routinely used tools for disease management (Lloyd-Smith et al., 2009a, Woolhouse, 2011).

A literature survey of modeling studies focusing on zoonotic diseases found that most of these studies are limited to dynamics of zoonoses in a single host species, either in the

reservoir animal species or human populations. They found only six studies that considered animal-to-human spillover for directly transmitted zoonotic disease, which is the most crucial phase of zoonotic dynamics (Lloyd-Smith et al., 2009b). Therefore there is a need to direct more modeling research on the zoonotic diseases at the animal-human interface, and how the spread at the interface would affect the spread and control measures in animal and human populations. Zoonoses is a broad topic consisting of a wide-spectrum of infectious agents with diverse and complex biology, life cycles, and host-species interactions. Amongst zoonotic diseases, pandemics caused by influenza A viruses still remains a major threat to mankind, occurring over the intervals of one to four decades since pandemic H1N1 in 1918 (Brown, 2000, Ma et al., 2009, Zimmer and Burke, 2009). It causes significant public health, livelihood and economic impact (Meltzer et al., 1999, Fiore et al., 2008). In addition, unlike many other directly transmitted zoonotic diseases where the transmission of a disease is limited to single host species after crossing the interspecies barrier, influenza A viruses circulating in swine and human population (H1, H2, H3 subtypes) have been shown easily transmissible between swine and people, particularly the pH1N1 virus. Therefore, for simplicity pH1N1 transmission dynamic at the swine-human interface and effect of control strategies were investigated as a case study for zoonotic diseases modeling.

1.1 Influenza viruses

Influenza viruses belong to a family Orthomyxoviridae and consist of three types, influenza A, B and C (Baigent and McCauley, 2003, Alexander, 2007). Influenza viruses

are made of a negative sense, single strand RNA genome divided into eight (type A and B) or seven (type C) linear segments. Influenza type A viruses can infect a range of mammalian and avian species naturally, while the type B is known to infect only humans and seals, and the type C infects humans and swine only. The influenza A and B viruses cause a wide range of severe respiratory diseases and occasionally encephalitis, whereas the type C only causes mild respiratory tract infection in the hosts (Baigent and McCauley, 2003, Alexander, 2007). Only the type A viruses have been associated with the major human influenza pandemics. Influenza A viruses are further classified into subtypes based on their two surface antigens, haemagglutinin (HA) and neuraminidase (NA). There are 17 HA (H1–H17) and 10 NA (N1–N10) subtypes, with a particular virus containing one each of HA and NA antigens in any combinations, thus resulting in many subtypes (Baigent and McCauley, 2003, Alexander, 2007, Tong et al., 2012). The aquatic birds (waterfowl, shorebirds and gulls) are the natural reservoir of influenza viruses from which mammalian influenza viruses are directly or indirectly derived (Hinshaw et al., 1981, Baigent and McCauley, 2003, Alexander, 2007). To date human viruses are limited to H1, H2, H3, N1 and N2 subtypes, whereas only H5 and H7 are known to cause highly pathogenic avian influenza (HPAI) in birds. Low pathogenic H5 and H7 viruses also exist in birds. The main influenza viruses circulating in swine across the world include subtypes H1N1 (also known as ‘classical’ swine influenza virus), H1N2, H3N2 and pH1N1 2009 viruses (Torremorell et al., 2012). Although pigs can be infected with HPAI H5N1 virus, both field and experimental evidences show they are

less susceptible to the virus (Lipatov et al., 2008, Cao et al., 2013). However, some evidence of the virus circulating in pigs at low prevalence without exhibiting clinical signs has been reported, indicating the virus may be adapting to pigs (Nidom et al., 2010). Its adaption to pigs is further reinforced by the experimental evidence where the H5N1 viruses isolated from pigs in Indonesia were found less harmful to mice than the viruses isolated from chickens (Takano et al., 2009). If H5N1 viruses adapt to pigs, a novel virus of pandemic potential may evolve over time through reassortment with other influenza viruses circulating in pigs at the same.

The evolution of different influenza virus subtypes occurs as a result of the molecular changes in the eight RNA segments by: (i) point mutations or antigenic drift - resulting from changes in the antigenic sites of HA and NA surface proteins, and (ii) gene reassortment or antigenic shift that results from the introduction of HA and/or NA genes from an animal-derived influenza virus to the circulating human virus, generating a novel influenza A subtypes. This antigenic shift is responsible for causing major influenza pandemics, whereas the antigenic drift causes seasonal influenza epidemics. Recently human infections have also resulted from complete avian viruses causing fatalities (H5N1 and H7N9) or non-fatal diseases (H7N7 and H9N2) (Baigent and McCauley, 2003, Alexander, 2007, Gao et al., 2013, Uyeki and Cox, 2013). A comprehensive review on avian influenza viruses and factors associated with virus virulence, host-diversity and cross-species transmission of influenza A viruses in

humans are provided by Alexander (2007) and Baigent and McCauley (2003), respectively.

The first anecdotal evidence of epizootic influenza outbreak in swine prior to the influenza pandemic in 1918 was documented in England in 1892, coinciding with the influenza pandemic of 1889 (Baigent and McCauley, 2003, Morens and Taubenberger, 2013). Before 1892, influenza outbreaks have been reported mainly in equine (from 1647 to 1917) often associated temporally and geographically to epidemics of human influenza. This shift in the epizootiological patterns of influenza from horse to swine after 1918 has been speculated as a result of co-adaptation of human influenza A viruses to domestic mammals in close proximity to each other and to humans, coinciding with the intensification of swine production in modern era with relative decrease in equine population and human-equine interaction (Morens and Taubenberger, 2013).

Since the first report of transmission of the H1N1 1918 virus from humans-to-pigs (Shope, 1931), the transmission of influenza A viruses between people and swine has been well documented (Hinshaw et al., 1978, Easterday, 1980, Dacso et al., 1984, Myers et al., 2007). Pigs can be infected by both avian and human influenza viruses. There is much evidence of reassortments of swine, human and avian influenza viruses occurring in pigs in Europe (Brown et al., 1998) and in North America (Zhou et al., 1999, Karasin et al., 2000, Lekcharoensuk et al., 2006, Olsen et al., 2006). The transmission of influenza viruses from pigs to people were commonly reported (Brown, 2000, Myers et al., 2007, Robinson et al., 2007, Ma et al., 2009, Zimmer and Burke, 2009). The pH1N1

also rapidly spread from humans to swine since its first case reported on a swine farm in Alberta, Canada (Howden et al., 2009). Several reverse zoonosis of pH1N1 continue to be reported from across the world (Hofshagen et al., 2009, OIE, 2009-2010, Song et al., 2010, Forgie et al., 2011, Nelson et al., 2012, Torremorell et al., 2012). Recently the transmission of the H3N2 variant from pigs-to-humans, and a subsequent limited spread between humans, was reported in the United States (US) (Lindstrom et al., 2012). Cross-sectional serological studies found that occupations involving direct contact with pigs (e.g. swine-farmers, veterinarians, abattoir-workers) are at higher risk of zoonotic influenza infection. Swine farmers are relatively at higher risk than veterinarians and abattoir-workers (Olsen et al., 2002, Myers et al., 2006). The persistent transmission pressure between swine and workers increases the opportunity for zoonotic spread of novel influenza viruses (Myers et al., 2006). As such, swine are considered to be potential hosts for the emergence of novel pandemic influenza viruses, and it is important to understand the transmission dynamics of influenza at the swine-human interface.

1.2 Modeling approaches to contagious diseases

Mathematical and computer simulation models are being widely used, inter alia, to investigate the patterns and extent of spread of diseases, evaluate intervention strategies, assess and develop contingency plans, and guide policy decision makers. Examples include, pandemic influenza (Longini et al., 2004, Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Halloran et al., 2008, Fraser et al., 2009) and severe acute

respiratory syndrome (SARS) (Lipsitch et al., 2003, Lloyd-Smith et al., 2003, Riley et al., 2003, Gumel et al., 2004) in human populations, and the foot-and-mouth disease (FMD) outbreak of 2001 in the United Kingdom (Jalvingh et al., 1999, Ferguson et al., 2001c, Ferguson et al., 2001a, Morris et al., 2001, Shirley and Rushton, 2005a, Kiss et al., 2006b). Recently, rapid growth in the application of simulation models was observed mainly due to the UK FMD outbreak of 2001 and the emergence of zoonotic diseases such as SARS, H5N1, and pH1N1 (Lee et al., 2009b, Lloyd-Smith et al., 2009b). These diseases caused significant adverse socio-economic and animal welfare impacts, and notable public health concerns. Concurrently, modeling approaches have also become increasingly complex, evolving from simple deterministic compartmental models, also known as 'aggregate' or 'system dynamic' models (SDMs) (Mills et al., 2004, Arino et al., 2008, Brauer, 2008) to stochastic individual-based or agent-based models (ABMs) (Germann et al., 2006, Lee et al., 2009a, Yang et al., 2009, Tsai et al., 2010). Agent-based models offer the advantages of greater flexibility to incorporate individual-level heterogeneities such as age, sex, risk of susceptibility to an infection, historical health information (for example vaccination status, waning immunity, etc.) as well as spatial locations. In addition, tracing of infected individuals and its contacts, and targeted intervention measures can be easily implemented in this type of models. Some limitations of ABMs are: they are more computationally intensive and time consuming, difficulty in parameterization of a model as it require detail individual-level information (such as individual contact pattern, etc.), which are often difficult to collect, and

difficulty to perform sensitivity analyses (Brauer, 2008, Gojovic et al., 2009).A growing number of modeling studies have also extended the individual-based models further by explicitly incorporating either empirical or theoretical networks for disease spread and intervention measures in human populations (Riley et al., 2003, Eubank et al., 2004, Shirley and Rushton, 2005b, Rahmandad and Sterman, 2008) and animal populations (Green et al., 2006, Kao et al., 2006, Kiss et al., 2006b, Kiss et al., 2006a, Kiss et al., 2008, Sharkey et al., 2008, Vernon and Keeling, 2009, Dürr et al., 2013, Fournié et al., 2013). As individuals have contacts only with a limited set of other individuals in a population (although this number can vary widely), network models based on scale-free, small-world or spatial networks add more realism to the system being modeled compared with random mixing models. Furthermore, the frequency and patterns of these contacts will represent different network topologies influencing a disease spread and effectiveness of disease control strategies in a population. The advancement in the modeling approaches is facilitated by the availability of modern high-power computers, advanced modeling software and increasing data being available (Morris et al., 2001, Rahmandad and Sterman, 2008, Lloyd-Smith et al., 2009b, Vernon and Keeling, 2009, Stevenson et al., 2013).

Simulation models enable researchers to simulate thousands of virtual ‘what if’ experiments of disease outbreaks and evaluate the effectiveness of control strategies under a range of scenarios. Such experiments cannot be implemented in real-world situations for ethical, economical and logistical reasons (Keeling and Rohani, 2008,

Lloyd-Smith et al., 2009b, Vynnycky and White, 2010). Through these experiments, modelers can examine in detail the effects of parameters of interest, be they represent population dynamics, biological factors, or disease control. The fact that they are an abstract and simplified representation of a real-world, models have been used meaningfully to support policy decisions both at the national level during the FMD outbreak of 2001 in UK (Jalvingh et al., 1999, Ferguson et al., 2001b, Morris et al., 2001), and at the global level for SARS (Lipsitch et al., 2003, Lloyd-Smith et al., 2003, Riley et al., 2003, Gumel et al., 2004, Hsieh et al., 2007) and pH1N1 outbreaks (air travel ban was avoided based on the findings of Cooper et al., (2006) and Hollingsworth et al., (2006).

1.3 Objectives

The objectives of this research relate to the application of simulation modeling of infectious zoonotic diseases. In particular, modeling the effect of the transmissibility of pH1N1 virus at the animal-human interface and its impact on disease spread was addressed as a broadly representative case study. The pH1N1 virus was chosen as an example because: (a) it is easily transmissible from human-to-human, swine-to-swine and between human and swine populations, (b) information about the biology of this virus is relatively abundant, and (c) there were several questions arising from pH1N1 concerning its dynamics at the human-to-swine interface.

Specifically, the research objectives were to:

- Carry out a systematic review of different modeling methods and approaches for zoonotic influenza in human and animal populations, particularly those related to the animal-human interface, and identify gaps in the knowledge of influenza transmission dynamics in animals and at the animal-human interface. Furthermore, it was also aimed to summarize parameters used in these modeling studies for ready reference in future works (Chapter 2).
- Assess the effects of the disease spread parameters on transmission between human and animal populations, and the benefit of targeted vaccination of swine-workers (Chapter 3).
- Assess the effectiveness of a combination of different intervention strategies such as the speed of detection of outbreaks, quarantine, movement control and ring vaccination strategies against the spread of the disease between swine, human, and swine and human populations (Chapter 4).
- Assess the feasibility of using NAADSM for modeling the spread and control of directly transmitted zoonotic diseases (Chapters 3 to 4).
- Carry out network analysis of swine shipments among farms to estimate farm and network level metrics, and parameters necessary for modeling of infectious diseases and supporting risk-based disease management strategies in swine populations in Ontario, Canada (Chapter 5).

- Assess the effects of network topologies (random, scale-free and small-world networks) on the spread and control of pH1N1 virus among farms using the agent-based network modeling approach (Chapter 6).

1.4 References

Alexander, D. J., 2007: An overview of the epidemiology of avian influenza. Vaccine, 25, 5637-5644.

Arino, J., F. Brauer, P. van den Driessche, J. Watmough and J. Wu, 2008: A model for influenza with vaccination and antiviral treatment. J. Theor. Biol., 253, 118-130.

Baigent, S. J. and J. W. McCauley, 2003: Influenza type A in humans, mammals and birds: determinants of virus virulence, host-range and interspecies transmission. Bioessays, 25, 657-671.

Brauer, F., 2008: Epidemic models with heterogeneous mixing and treatment. Bull. Math. Biol., 70, 1869-1885.

Brown, I. H., 2000: The epidemiology and evolution of influenza viruses in pigs. Vet. Microbiol., 74, 29-46.

Brown, I. H., P. A. Harris, J. W. McCauley and D. J. Alexander, 1998: Multiple genetic reassortment of avian and human influenza A viruses in European pigs, resulting in the emergence of an H1N2 virus of novel genotype. J. Gen. Virol., 79, pt. 12, 2947-2955.

Cao, N., W. Zhu, Y. Chen, L. Tan, P. Zhou, Z. Cao, C. Ke, Y. Li, J. Wu, W. Qi, P. Jiao and G. Zhang, 2013: Avian influenza A (H5N1) virus antibodies in pigs and residents of swine farms, southern China. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology, 58, 647-651.

Cooper, B. S., R. J. Pitman, W. J. Edmunds and N. J. Gay, 2006: Delaying the international spread of pandemic influenza. PLoS Med., 3, e212-e212.

Dacso, C. C., R. B. Couch, H. R. Six, J. F. Young, J. M. Quarles and J. A. Kasel, 1984: Sporadic occurrence of zoonotic swine influenza virus infections. J. Clin. Microbiol., 20, 833-835.

Dürr, S., H. zu Dohna, E. Di Labio, T. E. Carpenter and M. G. Doherr, 2013: Evaluation of control and surveillance strategies for classical swine fever using a simulation model. Prev. Vet. Med., 108, 73-84.

Easterday, B. C., 1980: The epidemiology and ecology of swine influenza as a zoonotic disease. Comp. Immunol. Microbiol. Infect. Dis., 3, 105-109.

Eubank, S., H. Guclu, V. S. Anil Kumar, M. V. Marathe, A. Srinivasan, Z. Toroczkai and N. Wang, 2004: Modelling disease outbreaks in realistic urban social networks. Nature, 429, 180-184.

Ferguson, N. M., D. A. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn and D. S. Burke, 2005: Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature, 437, 209-214.

Ferguson, N. M., D. A. T. Cummings, C. Fraser, J. C. Cajka, P. C. Cooley and D. S. Burke, 2006: Strategies for mitigating an influenza pandemic. Nature, 442, 448-452.

Ferguson, N. M., C. A. Donnelly and R. M. Anderson, 2001a: The foot-and-mouth epidemic in Great Britain: Pattern of spread and impact of interventions. Science, 292, 1155-1160.

Ferguson, N. M., C. A. Donnelly and R. M. Anderson, 2001b: The foot-and-mouth epidemic in Great Britain: pattern of spread and impact of interventions. Science, 292, 1155-1160.

Ferguson, N. M., C. A. Donnelly and R. M. Anderson, 2001c: Transmission intensity and impact of control policies on the foot and mouth epidemic in Great Britain. Nature, 413, 542-548.

Fiore, A., D. Shay, K. Broder, J. Iskander, T. Uyeki, G. Mootrey, J. Bresee and N. Cox, 2008: Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR, 57, 1-60.

Forgie, S. E., J. Keenliside, C. Wilkinson, R. Webby, P. Lu, O. Sorensen, K. Fonseca, S. Barman, A. Rubrum, E. Stigger, T. J. Marrie, F. Marshall, D. W. Spady, J. Hu, M. Loeb, M. L. Russell and L. A. Babiuk, 2011: Swine outbreak of pandemic influenza A virus on a Canadian research farm supports human-to-swine transmission. Clin. Infect. Dis., 52, 10-18.

Fournié, G., J. Guitian, S. Desvaux, V. C. Cuong, D. H. Dung, D. U. Pfeiffer, P. Mangtani and A. C. Ghani, 2013: Interventions for avian influenza A (H5N1) risk management in live bird market networks. Proc. Natl. Acad. Sci. U. S. A., 110, 9177-9182.

Fraser, C., C. A. Donnelly, S. Cauchemez, W. P. Hanage, M. D. Van Kerkhove, T. D. i. Hollingsworth, J. Griffin, R. F. Baggaley, H. E. Jenkins, E. J. Lyons, T. Jombart, W. R. Hinsley, N. C. Grassly, F. Balloux, A. C. Ghani, N. M. Ferguson, A. Rambaut, O. G. Pybus, H. Lopez-Gatell, C. M. Alpuche-Aranda, I. B. Chapela, E. P. Zavala, D. M. E. Guevara, F. Checchi, E. Garcia, S. Hugonnet and C. Roth, 2009: Pandemic potential of a strain of influenza A (H1N1): Early findings. Science, 324, 1557-1561.

Gao, R., B. Cao, Y. Hu, Z. Feng, D. Wang, W. Hu, J. Chen, Z. Jie, H. Qiu, K. Xu, X. Xu, H. Lu, W. Zhu, Z. Gao, N. Xiang, Y. Shen, Z. He, Y. Gu, Z. Zhang, Y. Yang, X. Zhao, L. Zhou, X. Li, S. Zou, Y. Zhang, X. Li, L. Yang, J. Guo, J. Dong, Q. Li, L. Dong, Y. Zhu, T. Bai, S. Wang, P. Hao, W. Yang, Y. Zhang, J.

Han, H. Yu, D. Li, G. F. Gao, G. Wu, Y. Wang, Z. Yuan and Y. Shu, 2013: Human infection with a novel avian-origin influenza A (H7N9) virus. N. Engl. J. Med., 368, 1888-1897.

Germann, T. C., K. Kadau, I. M. Longini, Jr. and C. A. Macken, 2006: Mitigation strategies for pandemic influenza in the United States. Proc. Natl. Acad. Sci. U. S. A., 103, 5935-5940.

Green, D. M., I. Z. Kiss and R. R. Kao, 2006: Modelling the initial spread of foot-and-mouth disease through animal movements. Proc. R. Soc. Lond. B. Biol. Sci., 273, 2729-2735.

Gumel, A. B., S. Ruan, T. Day, J. Watmough, F. Brauer, P. van den Driessche, D. Gabrielson, C. Bowman, M. E. Alexander, S. Ardal, J. Wu and B. M. Sahai, 2004: Modelling strategies for controlling SARS outbreaks. Proc. R. Soc. Lond. B. Biol. Sci., 271, 2223-2232.

Halloran, M. E., N. M. Ferguson, S. Eubank, I. M. Longini, Jr., D. A. T. Cummings, B. Lewis, S. Xu, C. Fraser, A. Vullikanti, T. C. Germann, D. Wagener, R. Beckman, K. Kadau, C. Barrett, C. A. Macken, D. S. Burke and P. Cooley, 2008: Modeling targeted layered containment of an influenza pandemic in the United States. Proc. Natl. Acad. Sci. U. S. A., 105, 4639-4644.

Hinshaw, V. S., J. Bean Jr., R. G. Webster and B. C. Easterday, 1978: The prevalence of infuenza viruses in swine and the antigenic and genetic relatedness of infuenza viruses from man to swine. Virology, 84, 51- 62.

Hinshaw, V. S., R. G. Webster, B. C. Easterday and W. J. Bean, Jr., 1981: Replication of avian influenza A viruses in mammals. Infect. Immun., 34, 354-361.

Hofshagen, M., B. Gjerset, C. Er, A. Tarpai, E. Brun, B. Dannevig, T. Bruheim, I. G. Fostad, B. Iversen, O. Hungnes and B. Lium, 2009: Pandemic influenza A(H1N1)v: human to pig transmission in Norway? Euro Surveill., 14.

Hollingsworth, T. D., N. M. Ferguson and R. M. Anderson, 2006: Will travel restrictions control the international spread of pandemic influenza? Nat. Med., 12, 497-499.

Howden, K. J., E. J. Brockhoff, F. D. Caya, L. J. McLeod, M. Lavoie, J. D. Ing, J. M. Bystrom, S. Alexandersen, J. M. Pasick, Y. Berhane, M. E. Morrison, J. M. Keenliside, S. Laurendeau and E. B. Rohonczy, 2009: An investigation into human pandemic influenza virus (H1N1) 2009 on an Alberta swine farm. Can. Vet. J., 50, 1153-1161.

Hsieh, Y. H., P. van den Driessche and L. Wang, 2007: Impact of travel between patches for spatial spread of disease. Bull. Math. Biol., 69, 1355-1375.

Jalvingh, A. W., M. Nielen, H. Maurice, A. J. Stegeman, A. R. W. Elbers and A. A. Dijkhuizen, 1999: Spatial and stochastic simulation to evaluate the impact of

events and control measures on the 1997–1998 classical swine fever epidemic in The Netherlands.: I. Description of simulation model. Prev. Vet. Med., 42, 271-295.

Jones, K. E., N. G. Patel, M. A. Levy, A. Storeygard, D. Balk, J. L. Gittleman and P. Daszak, 2008: Global trends in emerging infectious diseases. Nature, 451, 990-993.

Kao, R. R., L. Danon, D. M. Green and I. Z. Kiss, 2006: Demographic structure and pathogen dynamics on the network of livestock movements in Great Britain. Proc. R. Soc. Lond. B. Biol. Sci., 273, 1999-2007.

Karasin, A. I., M. M. Schutten, L. A. Cooper, C. B. Smith, K. Subbarao, G. A. Anderson, S. Carman and C. W. Olsen, 2000: Genetic characterization of H3N2 influenza viruses isolated from pigs in North America, 1977-1999: evidence for wholly human and reassortant virus genotypes. Virus Res., 68, 71-85.

Keeling, M. and P. Rohani, 2008: Modeling infectious diseases in humans and animals. pp. 1-13, 15-52. Princeton University Press, Princeton, New Jersey.

Kiss, I. Z., D. M. Green and R. R. Kao, 2006a: Infectious disease control using contact tracing in random and scale-free networks. J. R. Soc. Interface, 3, 55-62.

Kiss, I. Z., D. M. Green and R. R. Kao, 2006b: The network of sheep movements within Great Britain: Network properties and their implications for infectious disease spread. J. R. Soc. Interface, 3, 669-677.

Kiss, I. Z., D. M. Green and R. R. Kao, 2008: The effect of network mixing patterns on epidemic dynamics and the efficacy of disease contact tracing. J. R. Soc. Interface, 5, 791-799.

Kuiken, T., E. C. Holmes, J. McCauley, G. F. Rimmelzwaan, C. S. Williams and B. T. Grenfell, 2006: Host species barriers to influenza virus infections. pp. 394-397.

Lee, B. Y., S. T. Brown, P. Cooley, M. A. Potter, W. D. Wheaton, R. E. Voorhees, S. Stebbins, J. J. Grefenstette, S. M. Zimmer, R. K. Zimmerman, T. M. Assi, R. R. Bailey, D. K. Wagener and D. S. Burke, 2009a: Simulating School Closure Strategies to Mitigate an Influenza Epidemic. J. Public Health Manag. Pract.

Lee, V. J., D. C. Lye and A. Wilder-Smith, 2009b: Combination strategies for pandemic influenza response - a systematic review of mathematical modeling studies. BMC Med., 7, 76.

Lekcharoensuk, P., K. M. Lager, R. Vemulapalli, M. Woodruff, A. L. Vincent and J. A. Richt, 2006: Novel swine influenza virus subtype H3N1, United States. Emerg. Infect. Dis., 12, 787–794.

Lipatov, A. S., Y. K. Kwon, L. V. Sarmento, K. M. Lager, E. Spackman, D. L. Suarez and D. E. Swayne, 2008: Domestic pigs have low susceptibility to H5N1 highly pathogenic avian influenza viruses. PLoS Pathog, 4, e1000102.

Lipsitch, M., T. Cohen, B. Cooper, J. M. Robins, S. Ma, L. James, G. Gopalakrishna, S. K. Chew, C. C. Tan, M. H. Samore, D. Fisman and M. Murray, 2003: Transmission dynamics and control of severe acute respiratory syndrome. Science, 300, 1966-1970.

Lloyd-Smith, J. O., A. P. Galvani and W. M. Getz, 2003: Curtailing transmission of severe acute respiratory syndrome within a community and its hospital. Proc. R. Soc. Lond. B. Biol. Sci., 270, 1979-1989.

Lloyd-Smith, J. O., D. George, K. M. Pepin, V. E. Pitzer, J. R. Pulliam, A. P. Dobson, P. J. Hudson and B. T. Grenfell, 2009a: Epidemic dynamics at the human-animal interface. Science, 326, 1362-1367.

Lloyd-Smith, J. O., D. George, K. M. Pepin, V. E. Pitzer, J. R. C. Pulliam, A. P. Dobson, P. J. Hudson and B. T. Grenfell, 2009b: Epidemic Dynamics at the Human-Animal Interface. Science, 326, 1362-1367.

Longini, I. M., Jr., M. E. Halloran, A. Nizam and Y. Yang, 2004: Containing pandemic influenza with antiviral agents. Am. J. Epidemiol., 159, 623-633.

Longini, I. M., Jr., A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D. A. Cummings and M. E. Halloran, 2005: Containing pandemic influenza at the source. Science, 309, 1083-1087.

Ma, W., K. M. Lager, A. L. Vincent, B. H. Janke, M. R. Gramer and J. A. Richt, 2009: The role of swine in the generation of novel influenza viruses. Zoonoses Public Health, 56, 326–337.

Meltzer, M. I., N. J. Cox and K. Fukuda, 1999: The economic impact of pandemic influenza in the United States: priorities for intervention. Emerg. Infect. Dis., 5, 659-671.

Mills, C. E., J. M. Robins and M. Lipsitch, 2004: Transmissibility of 1918 pandemic influenza. pp. 904 - 906.

Morens, D. M. and J. K. Taubenberger, 2013: A possible outbreak of swine influenza, 1892. Lancet Infect Dis.

Morris, R. S., J. W. Wilesmith, M. W. Stern, R. L. Sanson and M. A. Stevenson, 2001: Predictive spatial modelling of alternative control strategies for the foot-and-mouth disease epidemic in Great Britain, 2001. Vet. Rec., 149, 137-144.

Myers, K. P., C. W. Olsen and G. C. Gray, 2007: Cases of swine influenza in humans: a review of the literature. Clin. Infect. Dis., 44, 1084-1088.

Myers, K. P., C. W. Olsen, S. F. Setterquist, A. W. Capuano, K. J. Donham, E. L. Thacker, J. A. Merchant and G. C. Gray, 2006: Are swine workers in the United States at increased risk of infection with zoonotic influenza virus? Clin. Infect. Dis., 42, 14-20.

Nelson, M. I., M. R. Gramer, A. L. Vincent and E. C. Holmes, 2012: Global transmission of influenza viruses from humans to swine. J. Gen. Virol., 93, 2195-2203.

Nidom, C. A., R. Takano, S. Yamada, Y. Sakai-Tagawa, S. Daulay, D. Aswadi, T. Suzuki, Y. Suzuki, K. Shinya, K. Iwatsuki-Horimoto, Y. Muramoto and Y. Kawaoka, 2010: Influenza A (H5N1) viruses from pigs, Indonesia. Emerg. Infect. Dis., 16, 1515-1523.

OIE, 2009-2010: World Animal Health Information Database: Weekly disease information. Available at http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/reportarchive (accessed on 22 April 2010). Paris.

Olsen, C. W., L. Brammer, B. C. Easterday, N. Arden, E. Belay, I. Baker and N. J. Cox, 2002: Serologic evidence of H1 swine influenza virus infection in swine farm residents and employees. Emerg. Infect. Dis., 8, 814-819.

Olsen, C. W., A. I. Karasin, S. Carman, Y. Li, N. Bastien, D. Ojkic, D. Alves, G. Charbonneau, B. M. Henning, D. E. Low, L. Burton and G. Broukhanski, 2006: Triple reassortant H3N2 influenza A viruses, Canada, 2005. Emerg. Infect. Dis., 12, 1132-1135.

Rahmandad, H. and J. Sterman, 2008: Heterogeneity and network structure in the dynamics of diffusion: Comparing agent-based and differential equation models. Manage Sci, 54, 998–1014.

Riley, S., C. Fraser, C. A. Donnelly, A. C. Ghani, L. J. Abu-Raddad, A. J. Hedley, G. M. Leung, L. M. Ho, T. H. Lam, T. Q. Thach, P. Chau, K. P. Chan, S. V. Lo, P. Y. Leung, T. Tsang, W. Ho, K. H. Lee, E. M. Lau, N. M. Ferguson and R. M. Anderson, 2003: Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. Science, 300, 1961-1966.

Robinson, J. L., B. E. Lee, J. Patel, N. Bastien, K. Grimsrud, R. F. Seal, R. King, F. Marshall and Y. Li, 2007: Swine influenza (H3N2) infection in a child and possible community transmission, Canada. Emerg. Infect. Dis., 13, 1865-1870.

Sharkey, K. J., R. G. Bowers, K. L. Morgan, S. E. Robinson and R. M. Christley, 2008: Epidemiological consequences of an incursion of highly pathogenic H5N1 avian influenza into the British poultry flock. Proc. R. Soc. Lond. B. Biol. Sci., 275, 19-28.

Shirley, M. D. and S. P. Rushton, 2005a: Where diseases and networks collide: lessons to be learnt from a study of the 2001 foot-and-mouth disease epidemic. Epidemiol. Infect., 133, 1023-1032.

Shirley, M. D. F. and S. P. Rushton, 2005b: The impacts of network topology on disease spread. Ecol. Complexity, 2, 287-299.

Shope, R. E., 1931: Swine influenza : iii. Filtration experiments and etiology. J. Exp. Med., 54, 373-385.

Song, M. S., J. H. Lee, P. N. Pascua, Y. H. Baek, H. I. Kwon, K. J. Park, H. W. Choi, Y. K. Shin, J. Y. Song, C. J. Kim and Y. K. Choi, 2010: Evidence of human-to-swine transmission of the pandemic (H1N1) 2009 influenza virus in South Korea. J. Clin. Microbiol., 48, 3204-3211.

Stevenson, M. A., R. L. Sanson, M. W. Stern, B. D. O'Leary, M. Sujau, N. Moles-Benfell and R. S. Morris, 2013: InterSpread Plus: a spatial and stochastic simulation model of disease in animal populations. Prev. Vet. Med., 109, 10-24.

Takano, R., C. A. Nidom, M. Kiso, Y. Muramoto, S. Yamada, K. Shinya, Y. Sakai-Tagawa and Y. Kawaoka, 2009: A comparison of the pathogenicity of avian and swine H5N1 influenza viruses in Indonesia. Arch. Virol., 154, 677-681.

Tong, S., Y. Li, P. Rivailler, C. Conrardy, D. A. Castillo, L. M. Chen, S. Recuenco, J. A. Ellison, C. T. Davis, I. A. York, A. S. Turmelle, D. Moran, S. Rogers, M. Shi, Y. Tao, M. R. Weil, K. Tang, L. A. Rowe, S. Sammons, X. Xu, M. Frace, K. A. Lindblade, N. J. Cox, L. J. Anderson, C. E. Rupprecht and R. O. Donis, 2012: A distinct lineage of influenza A virus from bats. Proc. Natl. Acad. Sci. U. S. A., 109, 4269-4274.

Torremorell, M., M. Allerson, C. Corzo, A. Diaz and M. Gramer, 2012: Transmission of influenza A virus in pigs. Transbound. Emerg. Dis., 59, 68–84.

Tsai, M. T., T. C. Chern, J. H. Chuang, C. W. Hsueh, H. S. Kuo, C. J. Liau, S. Riley, B. J. Shen, D. W. Wang, C. H. Shen and T. S. Hsu Corresponding Author, 2010: Efficient simulation of the spatial transmission dynamics of influenza. PLoS Curr. Influenza, RRN1141.

Uyeki, T. M. and N. J. Cox, 2013: Global concerns regarding novel influenza A (H7N9) virus infections. N. Engl. J. Med., 368, 1862-1864.

Vernon, M. C. and M. J. Keeling, 2009: Representing the UK's cattle herd as static and dynamic networks. Proc. R. Soc. Lond. B. Biol. Sci., 276, 469-476.

Vynnycky, E. and R. White, 2010: An introduction to infectious disease modelling. Oxford University Press, Oxford, UK.

Woolhouse, M., 2011: How to make predictions about future infectious disease risks. Proc. R. Soc. Lond. B. Biol. Sci., 366, 2045-2054.

Woolhouse, M. E. and S. Gowtage-Sequeria, 2005: Host range and emerging and reemerging pathogens. Emerg. Infect. Dis., 11, 1842-1847.

Yang, Y., J. D. Sugimoto, M. E. Halloran, N. E. Basta, D. L. Chao, L. Matrajt, G. Potter, E. Kenah and I. M. Longini, Jr., 2009: The transmissibility and control of Pandemic Influenza A (H1N1) virus. Science, 326, 729-733.

Zhou, N. N., D. A. Senne, J. S. Landgraf, S. L. Swenson, G. Erickson, K. Rossow, L. Liu, K. Yoon, S. Krauss and R. G. Webster, 1999: Genetic reassortment of avian, swine, and human influenza A viruses in American pigs. J. Virol., 73, 8851-8856.

Zimmer, S. M. and D. S. Burke, 2009: Historical perspective-Emergence of influenza A (H1N1) viruses. N. Engl. J. Med., 361, 279-285.

Chapter 2

A Review of Simulation Modeling Approaches used for the Spread of Zoonotic Influenza Viruses in Animal and Human Populations*

* Dorjee, S., Z. Poljak, C. W. Revie, J. Bridgland, B. McNab, E. Leger and J. Sanchez, 2013: A review of simulation modeling approaches used for the spread of zoonotic influenza viruses in animal and human populations. Zoonoses and Public Health, 60, 383-411

2.1 Abstract

Increasing incidences of emerging and re-emerging diseases that are mostly zoonotic (e.g. SARS, avian influenza H5N1, pandemic influenza) have led to the need for a multidisciplinary approach to tackling these threats to public and animal health. Accordingly, a global movement of "One-Health/"One-Medicine" have been launched to foster collaborative efforts amongst animal and human health officials and researchers to address these problems. Historical evidence points to the fact that pandemics caused by influenza A viruses remain a major zoonotic threat to mankind. Recently a range of mathematical and computer simulation modeling methods and tools have increasingly been applied to improve our understanding of disease transmission dynamics, contingency planning and to support policy decisions on disease outbreak management. This review provides an overview of methods, approaches and software used for modeling the spread of zoonotic influenza viruses in animals and humans, particularly those related to the animal-human interface. Modeling parameters used in these studies are summarized to provide references for future work. This review highlights the limited application of modeling research to influenza in animals and at the animal-human interface, in marked contrast to the large volume of its research in human populations. Although, swine are widely recognized as a potential host for generating novel influenza viruses, and some of these viruses, including pandemic influenza A/H1N1 2009, have been shown to be readily transmissible between humans and swine, only one study was found related to the modeling of influenza spread at the swine-

human interface. Significant gaps in the knowledge of frequency of novel viral strains evolution in pigs, farm-level natural history of influenza infection, incidences of influenza transmission between farms and between swine and humans are clearly evident. Therefore, there is a need to direct additional research to the study of influenza transmission dynamics in animals and at the animal-human interface.

Keywords: Simulation models; modeling; zoonotic;influenza; parameters; software

2.2 Introduction

Mathematical and computer simulation models are increasingly being used to characterize the transmission dynamics of infectious diseases, to evaluate the effectiveness of various intervention strategies and to guide policy decisions on disease outbreak management. Examples include, the UK foot-and-mouth disease (FMD) outbreak in 2001(Ferguson et al., 2001b, Ferguson et al., 2001a, Keeling et al., 2001, Morris et al., 2001), severe acute respiratory syndrome (SARS) in 2003 (Lipsitch et al., 2003, Lloyd-Smith et al., 2003, Riley et al., 2003, Gumel et al., 2004), and pandemic influenza (Longini et al., 2004, Ferguson et al., 2005, Longini et al., 2005, 2006, Flahault et al., 2006, Germann et al., 2006, Halloran et al., 2008, Flahault et al., 2009, Fraser et al., 2009, Gojovic et al., 2009, Yang et al., 2009). The application of disease modeling has grown significantly since 2003 following the outbreaks of SARS and the highly pathogenic avian influenza (HPAI) epidemics caused by the H5N1 virus in Asia (from its perceived threat of generating a pandemic influenza strain) as highlighted by

Lloyd-Smith et al. (2009) and Keeling and Rohani (2008), and more recently after pH1N1 2009 outbreak. Models have also become increasingly complex, evolving from simple deterministic compartmental models (Mills et al., 2004, Arino et al., 2008, Brauer, 2008) to stochastic individual-based models (Germann et al., 2006, Carpenter and Sattenspiel, 2009, Yang et al., 2009, Lee et al., 2010a, Tsai et al., 2010); with stochastic individual-based network models (Ajelli and Merler, 2008, Davey et al., 2008, Chao et al., 2010) adding ever more realism through the use of computer simulation.

The emergence of zoonotic diseases such as SARS, HPAI caused by H5N1 and pH1N1 2009, together with the recognition that 58% of known human pathogens (Woolhouse and Gowtage-Sequeria, 2005) and 60% of emerging infectious disease (Jones et al., 2008) are zoonotic diseases has heightened research interest in zoonosis. Recognizing the need for a multidisciplinary approach in tackling these emerging public health concerns, a global movement on "One-Health / One-Medicine" was initiated to foster and facilitate collaborative efforts amongst animal and human health professionals (Harper et al., 2004). Historical evidence points to the fact that pandemics from influenza A viruses still remain one of the major zoonotic threats to mankind, occurring over intervals of one to four decades since pandemic influenza caused by H1N1 in 1918 (Brown, 2000, Ma et al., 2009, Zimmer and Burke, 2009), with significant public health, livelihood and economic consequences (Meltzer et al., 1999, Fiore et al., 2008). The pH1N1 2009 also rapidly spread from humans to swine, with the first case reported on a

swine farm in Alberta, Canada on 28 April 2009 (OIE, 2009). This was linked to a carpenter employed in a swine barn, who was infected with the virus during his trip to Mexico (Howden et al., 2009). Subsequently, several other countries reported outbreaks in swine (20 countries as of 28 April 2010), while cases were also reported on two turkey farms in Chile and one in Canada (OIE, 2009-2010). Human-to-swine transmission was suspected in almost all these outbreaks based on circumstantial evidence, with swine workers showing flu symptoms prior to outbreaks in swine (OIE, 2009-2010). Furthermore, pH1N1 2009 virus transmission between pigs was demonstrated under experimental (Itoh et al., 2009, Lange et al., 2009, Vincent et al., 2009, Brookes et al., 2010) and observational studies (Howden et al., 2009, Lange et al., 2009, Pasma and Joseph, 2010). No back transmission from pigs to humans was reported except for one suspected case in Canada (Howden et al., 2009). However, this may be related to the lack of reporting systems for pH1N1 2009 humans cases acquired from pigs. This virus demonstrated the potential for the pandemic influenza viruses with swine influenza gene lineage to emerge and spread between humans and swine readily (Vincent et al., 2010). Recently, a novel swine-origin influenza A H3N2 variant virus (designated as A(H3N2)v) containing the matrix gene derived from pH1N1 2009 virus was detected in humans in the US raising concern over the pandemic potential of these viruses of swine origin (Lindstrom et al., 2012) . It is therefore imperative to investigate epidemiological parameters influencing the transmission dynamics of pandemic influenza viruses at the swine-human interface. Similarly it is important to identify

appropriate surveillance or early warning systems, and intervention strategies to respond effectively to future outbreaks. Computer simulation modeling is a useful tool for such studies.

It would be of interest to know the extent of modeling research directed towards zoonotic influenza at the animal-human interface as zoonotic diseases present a continuing threat to public health. In addition the role that birds and swine play in the generation of new viral strains and their transmission to humans is important in model development. Therefore, this review consolidates the relevant literature on the modeling of influenza virus spread in animals (including birds) and humans. It provides an inventory of methods and approaches, including software/platforms used to model influenza viruses in animal and human populations, with a particular emphasis on spread at the animal-human interface. Any differences and challenges that may exist for modeling spread of influenza between animals and humans simultaneously are also investigated. The review also identifies parameters required for modeling influenza spread between animals and humans. This should facilitate the modeling process under a range of conditions by providing parameters and methods that may be relevant under different emerging influenza epidemic or pandemic situations.

2.3 Materials and Methods

In this review, mathematical or computer simulation models refer to dynamic disease transmission models where force of infection varies with changes in the prevalence of infectious and susceptible individuals in a population over time. This differs from many

statistical models where population status and parameter values remain fixed and are used to quantify association between outcome and explanatory variables (Dohoo et al., 2009, Vynnycky and White, 2010) .

2.3.1 Search strategy

A standard search term was developed based on the review objectives to collect information on the following research questions: (a) what are the different approaches and types of mathematical or computer simulation models used to model the spread of zoonotic influenza viruses in humans, animals or between animals and humans? (b) What modeling assumptions were used? (c) What software or platforms have been used? and (d) What were the parameters used for modeling influenza between animals and humans simultaneously? The search terms used across bibliographic databases were: ("mathematical model*" or "stochastic model*" or "deterministic model*" or "compartmental model*" or "epidemic model*" or "epidemiological model*" or "disease spread model*" or "simulation model*" or "transmission dynamic model*" or "agent-based model*" or "individual-based model*") and ("influenza" or "novel influenza" or "pandemic influenza" or "pandemic H1N1" or "novel H1N1" or H1N1 or H5N1 or "swine influenza" or "avian influenza" or "infectious diseases" or zoonosis or zoonoses or "zoonotic diseases"). Search fields were restricted to title and abstract while date of publication was used to exclude publications prior to 1990. Furthermore, search was limited to articles published in English. The searches were conducted on 9 February 2010 in the PubMed, CAB Abstract, ScienceDirect, and Agricola bibliographical

databases. All articles retrieved from each of these four databases were imported into the bibliographic reference package, EndNote® version X2 (Thomson, Reuters, Carlsbad, CA) and duplicate articles were removed. Additional relevant articles not captured by the search term, particularly articles related to experimental or observational studies that provided relevant parameters, were retrieved based on the references contained in some key articles.

2.3.2 Screening of articles

Titles and abstracts were screened for their relevance by two reviewers. Articles deemed to be "irrelevant", such as those related to other infectious or to non-infectious diseases of animals, humans, fish, or plants were removed. Articles were selected for review and data extraction if their abstract provided some details on mathematical or computer simulation models of influenza viruses in either animals, humans or both. Furthermore, if abstracts described the estimation of modeling parameters such as duration of disease states (incubation, latent, infectious, immune periods), contact parameters, transmission probabilities, the basic reproductive number (R_0) or generation intervals, these were also selected. Screening and selection of articles as to their relevance was reinforced using a predesigned data extraction template described below. To aid consistency in abstract screening, two reviewers pre-tested 15 articles and accepted or rejected articles were compared. Of these in only one case (Perlroth et al., 2010) did the reviewers come to a different conclusion on acceptance. On investigation it was seen that the confusion in this case was due to the fact that no guidance had been given for articles primarily

focused on evaluating cost impacts of mitigation strategies. As this article also provided useful modeling parameters it was decided that it should be included. The screening criteria were further refined to provide guidance for similar cases.

2.3.3 Data extraction

A template was developed in Microsoft Excel® version 2007 to aid in the extraction and recording of relevant information and parameters from each selected article. Detailed information on study objectives, questions of interest, study type, modeling methods and approaches, strain(s) of influenza virus(es), disease spread type (within or between species), population units, type(s) of intervention evaluated, software used were recorded. In addition, modeled disease spread parameters were extracted according to strain of influenza viruses and unit of population (individual, household, herd or flock levels).

2.3.4 Inventory of model types and approaches

A summary of different modeling approaches was generated based on the research questions addressed in the selected studies. Research questions of interests were grouped into five categories, those aimed at: parameter estimation (coded as P), evaluation of the spread of the disease (S), evaluation of different types of intervention (I), method development (M), and the development of a modeling software/platform or tool (T). Many articles addressed a combination of these questions, in which case the relevant combinations of categories was recorded. The inventory of models in this review also included broad categorizations as to whether they were stochastic or deterministic,

whether they were spatially explicit or not, and the type of contact structure modeled (homogeneous or heterogeneous mixing assumed or explicit contact network used).

For those unfamiliar with the range of modeling types and sometimes confusing terminology, a brief overview of some key approaches is provided below.

2.3.4.1 Deterministic model

A model in which a set of difference or differential equations (DE) describes the flow of individuals from one disease state to another as determined by a fixed set of parameters, and is sometimes referred as an aggregate or mean-field model. This approach will produce the same predicted outcome given a set of predefined model parameters (Nuño et al., 2007a, Arino et al., 2008, Brauer, 2008, Nuño et al., 2008).

2.3.4.2 Stochastic model

Stochastic models incorporate elements of random processes into the system. The infection and transition of individuals from one state to another is determined probabilistically (Ferguson et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Glass and Barnes, 2007, Ajelli and Merler, 2008, Halloran et al., 2008, Basta et al., 2009, Britton and Lindenstrand, 2009, Gojovic et al., 2009, Chao et al., 2010, Lee et al., 2010a). Model parameters (e.g. disease state duration, contact frequency, or probability of transmission per contact) are specified in the form of probability distributions, and values are randomly selected from these distributions for each iteration. Accordingly, the predicted outcomes also vary by iteration. Therefore, stochastic models are typically run many times (e.g. 1000 iterations) to obtain a reasonable distribution of potential

outcomes. The model types described below can be implemented in either a deterministic or stochastic manner.

2.3.4.3 Compartmental model

In a compartment model, individuals in the population are categorized into one or more subgroups (compartments) based on the similarity of certain characteristics, such as susceptibility to a particular infection, contact types and rates, and most importantly the individual's disease state (e.g. susceptible, infectious, and recovered which is why these are often referred to as "SIR" models). Infection process in the population is determined by the average behavior of the group, and individuals within each compartment are assumed to be homogenous and mixed perfectly. The flow of individuals from one compartment to another is determined by the sum of the individual's underlying probabilistic rate and the model tracks this on a collective basis during each time step of the simulation (Chowell et al., 2006a, Chowell et al., 2006b, Flahault et al., 2006, Hollingsworth et al., 2006, Nuño et al., 2007b, Vardavas et al., 2007, Arinaminpathy and McLean, 2008, Arino et al., 2008, Tsai et al., 2010, Tuite et al., 2010).

2.3.4.4 Agent-based / individual-based model

The disease transmission process in an agent-based or individual-based model is governed by the behavior of each individual. Rules governing disease transmission dynamics are defined at an individual level. Although the same disease states (susceptible / infectious / recovered) are used as in the compartmental model, they are only used to represent an individual's disease state at each time step of the simulation.

The model keeps track of each individual (rather than the group of individuals) and adds up individuals in each disease state at the end of each time-step of the simulation. Therefore, this type of model can capture heterogeneity of individual behavior (such as 'super-spreaders'- individuals who spread disease more readily than others as a result of a higher than average contact rate) and other sources of variation, which can have important impacts in terms of overall disease transmission dynamics. Incorporating such heterogeneity adds realism to the modeled process (Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Ohkusa and Sugawara, 2007, Basta et al., 2009, Yang et al., 2009, Yasuda and Suzuki, 2009).

2.3.4.5 Network model

Network models simulate disease spread in the population by explicitly taking into consideration the actual contact structures between individuals ('who is connected to whom'). Stochastic individual-based network models that simulate disease spread based on contact structures between individuals are more complex, yet more realistic, providing more accurate predictions. However, the reliability of these models depends on the availability of contact information which is still rare in most situations (Carrat et al., 2006, Ajelli and Merler, 2008, Davey et al., 2008, Chao et al., 2010, Perlroth et al., 2010).

2.3.4.6 Metapopulation model

A metapopulation model consists of a collection of distinct subpopulations of the same species each having its own distinct dynamics, and yet being connected to other

subpopulations through limited interactions. In this approach disease spread occurs through mobility or migration processes of individuals amongst subpopulations. These characteristics suggest that metapopulation modeling should provide a suitable approach for modeling the spread of pandemic influenza at global or regional levels via, for example, air travel (Cooper et al., 2006, Colizza et al., 2007, Balcan et al., 2009, Flahault et al., 2009).

2.3.4.7 Gravity model

The gravity model can be used to model disease spread between different geographical locations (for example, from one province to another) by explicitly incorporating rates of movement of people which are influenced by the population sizes and distances between locations. Increased movement tends to occur with greater population size and more closely linked areas when compared to less densely populated areas that are farther apart. This approach was used to investigate influenza spread from a large city (point of introduction) to other provinces in Vietnam (Boni et al., 2009).

2.3.4.8 Contact structure

Type and frequency of contacts between infectious and susceptible individuals is likely to play a crucial role in infectious disease transmission within a population, depending on the infectiousness and mode of transmission of the causative agent(s). Highly contagious diseases such as foot-and-mouth disease (FMD) can be transmitted over long distance through aerosol; similarly influenza or measles require less intimate contact than tuberculosis. In addition, the mixing pattern of hosts tends to play a crucial role in

the way disease is transmitted. The modeling of transmission characteristics will therefore be heavily influenced by assumptions around the homogeneity or heterogeneity of mixing. Homogeneous mixing assumes that contact between different individuals occurs randomly with equal probability (e.g. each child is equally likely to make contact with any other child or adult and vice versa). Heterogeneous mixing assumes non-random mixing where some individuals or groups are more likely to be in contact with infected individuals than others (Brauer, 2008, Vynnycky and White, 2010). Furthermore, heterogeneous mixing can be assortative or disassortative. In assortative mixing, individuals belonging to the same subgroup make more contacts amongst themselves than with members of other subgroups (e.g. children are more likely to mix with other children than with adults). Disassortative mixing occurs when members of one subgroup mix more readily with members of a different subgroup than with members from within their own subgroup (e.g. sexual partners). Subgroups can be defined based on any characteristic (e.g. age group, gender, occupation, etc.) that is considered important in explaining differences in disease transmission and control. It has been noted that the assumption of homogeneous mixing, present in many models, is unrealistically simple in most situations (Brauer, 2008, Vynnycky and White, 2010).

2.3.5 Intervention strategies

Approaches used for assessing different intervention strategies have been summarized into the following groups: antiviral treatment, including prophylactic use (coded as A), vaccination prior to or during outbreak (V), school or day-care closure (S), and social

distancing (D). This last category includes workplace closure, contact tracing, quarantine, isolation, cancellation of community and mass gathering, use of personal hygiene and protective equipment. In addition, movement control and depopulation of animals, including bird, are coded as (M), while air travel restrictions are coded as (T). A combination of these letters indicates that modeled assessment covered a combination of the respective intervention measures.

2.3.6 Modeling parameters

Parameters extracted have been summarized into three categories: (a) estimated values, where an article attempted to estimate parameters from empirical data taken from experimental, observational, or modeling studies; (b) referenced values, where values were taken from other articles; (c) assumed values, where values assumed for modeling purposes were based on either expert opinion or unpublished data sources. Furthermore, articles that estimated parameters with 95% confidence intervals are reported separately so as not to dilute them with values from other studies that only estimated mean, minimum and/or maximum values. Parameters were summarized as median and range (minimum and maximum values) of means, medians, minimum and maximum values from one or more articles. However, only summary estimates of means, minimum and maximum values are presented in the main text as very few median values were available for most parameters. A detailed summary of these estimates along with a list of articles and reference sources is provided in the Supplementary materials in Appendix A. Single values for a parameter (with no stated range) indicate that these were either

extracted from a single article or that the values were exactly the same when consolidated from two or more articles. If an article provided only a single value for a particular parameter then this was entered under the mean section. In the main text, parameters were summarized according to strain of influenza viruses. Studies that did not specify a particular virus strain but used general terms such as "novel influenza", "pandemic influenza" viruses, or "mutant form of avian influenza H5N1" have been grouped under “Novel influenza virus”. In addition, studies that investigated a novel influenza virus but calibrated model parameters to a known influenza viral strain were also grouped under a novel influenza virus category. If studies described the agent as a seasonal influenza virus (without specifying a particular strain) or the term "general influenza virus" was used, they were grouped under influenza viruses. Detailed summary according to the specific strain or terms used for different influenza strain along with article list are presented in the Supplementary materials in Appendix A. All data processing and summary analyses were carried out using Stata version 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP) after importing data from Microsoft Excel® version 2007.

2.4 Results and Discussion

2.4.1 Search strategy

A total of 721 unique articles were retrieved from PubMed, CAB Abstract, ScienceDirect and Agricola. Of these, 224 and 182 articles were excluded, through title and abstract screening respectively, as they were related to disease modeling and

epidemiological studies of other infectious or non-infectious diseases of animals, humans, fishes, and plants, including one article related to computer viruses. Of the 315 articles reviewed, data were extracted from 133 articles. The remaining 182 articles were related to general reviews of models, general infectious disease models, and an assessment of the economic impact of vaccine adjuvant from which no relevant parameters could be extracted. In addition, the references from 9 articles (van der Goot et al., 2005, Tiensin et al., 2007, van der Goot et al., 2007, Basta et al., 2009, Cowling et al., 2009, Milne et al., 2009, Tuite et al., 2009, Chao et al., 2010, Tuite et al., 2010) considered to be important recent outputs in the area were individually reviewed and from these a further 18 articles were identified and added to the set for data extraction.

From a total of 151 articles from which data were extracted, 93 and 11 articles were related to simulation modeling studies in humans and birds respectively, while 5 articles reported models of zoonotic transmission. The remaining 42 articles (comprising 28 on humans, 10 on animals and 4 on birds) were routine statistical and experimental studies, from which modeling parameters were extracted.

2.4.2 Inventory and general trend of modeling approaches

It was apparent that different approaches were applied to model influenza for a variety of purposes. This may be because influenza is a commonly occurring disease that is readily amenable to modeling and also because it can often be the cause of large-scale pandemics. A summary of the different model types applied to influenza viruses in animal and human populations to address a range of research questions of interest and

intervention measures are provided in Figure 2.1 and 2.2 respectively. Detailed list of articles that used different models to achieve different objectives are provided in Table S1 and S2 of the Supplementary materials. The temporal trend in the research questions of interest for modeling showed that the interests to assess intervention and influenza spread were predominant throughout the study period. In addition, an increasing number of articles related to method and tool development in combination with other questions of interest were observed since 2007 (Figure 2.3). An increasing trend in the publication of modeling studies was also observed since 2004, and this was mainly attributed to pandemic outbreaks of SARS and HPAI caused by H5N1, and more recently pH1N1 2009. The relatively lower number of modeling studies captured for 2010 was related to censoring of the review period on 19th February 2010. A similar or larger number of modeling studies published in 2010 would be expected as some of the articles related to pH1N1 2010 might have been published thereafter. The temporal trend of application of different modeling methods indicated that while compartmental models are still being used, increasing trends in the use of more complex models, such as individual-based and network models was observed since 2005 (Figure 2.4). This may be attributed to the availability of high power computers as well as availability of more complex modeling platforms. More details on research questions of interests and types of modeling approaches used in different populations are presented in the following section.

2.4.2.1 Humans

Modeling to evaluate different intervention strategies dominated this literature. Of the 93 modeling studies dealing with influenza in human populations, 38 and 25 focused on the evaluation of intervention strategies alone or in combination with other questions of interest respectively. Nine articles were solely aimed at parameter estimation (Mills et al., 2004, Chowell et al., 2006a, Sertsou et al., 2006, Chowell et al., 2007a, Chowell et al., 2008a, Chowell and Nishiura, 2008, Fraser et al., 2009, Lessler et al., 2009, Tuite et al., 2010); while three articles addressed parameter estimation and an assessment of the spread of influenza viruses (Massad et al., 2007, Ajelli and Merler, 2008, Colizza et al., 2009). Four articles described methods or approaches related to influenza modeling (Addy et al., 1991, Aparicio and Pascual, 2007, Fraser, 2007, Tsai et al., 2010) and four others on these methods or approaches in combination with influenza spread or the development of software (Brauer, 2008, Balcan et al., 2009, Carpenter and Sattenspiel, 2009, Chao et al., 2010). These new methods and approaches included: extending stochastic models to allow for variable length of infectious period and heterogeneity in contact rates (Addy et al., 1991); models to estimate the R_0 of within and between household transmission of influenza virus (Fraser, 2007); to improve computational efficiency of large-scale spatial stochastic individual-based models through algorithm refinement including the use of an R_0 parameter rather than per contact transmission probability (Tsai et al., 2010); and the development of aggregate (system dynamic) models that capture the influence of contact network structures using basic reproductive

ratios derived from the network structures (Aparicio and Pascual, 2007). Seven articles related solely to the spread of influenza (Flahault et al., 1994, Grais et al., 2003, Grais et al., 2004, Lavenu et al., 2004, Boni et al., 2009, Ohkusa and Sugawara, 2009, Rios-Doria and Chowell, 2009) and three focused on the development of modeling software (Hanley, 2006, Eichner et al., 2007, Feighner et al., 2009).

Some of the recent studies related to the development of methods and approaches in combination with other questions of interest are described below. Chao et al. (2010) developed the modeling platform FluTE for stochastic individual-based network models capable of simulating influenza spread across major metropolitan cities or even the entire population of the US, together with intervention measures. Lunelli et al. (2009) investigated the effects of incorporating contact matrices and spatial components (movements between geographic patches) into deterministic compartmental models and compared these with stochastic approaches. This was done to identify key elements of complexity to aid design decisions on achieving a balance between realism and computational efficiency. Deterministic models with heterogeneous mixing by partitioning populations into active and less active subgroups (Larson, 2007, Brauer, 2008) and a stochastic agent-based model for partitioning large-scale communities based on demographic, community features and daily activities (Das et al., 2008) were developed for assessing intervention strategies. Shaban et al. (2009) evaluated the effect of vaccination strategies at a household level during the early stage of an epidemic using a stochastic heterogeneous mixing compartmental model. An agent-based model to

examine the effect of population movement and seasonal community structure on the transmission of influenza was developed by Carpenter and Sattenspiel (2009). Nigmatulina and Larson (2009) used a deterministic compartmental model with heterogeneous mixing to examine the inclusion of behavioral feedback to capture the changing behavior of people due to perceived threats during the epidemic phase on the modeled effect of non-pharmaceutical intervention. The role of memory and adaptation on decision-making around vaccination coverage based on two incentives (commitment and family incentive) was assessed by Vardavas et al. (2007) using a deterministic homogeneous mixing compartmental model. The effect of different mobility networks (long-range air travel versus short-range commuting patterns) on the global and local spread of influenza epidemics was investigated using stochastic SEIR metapopulation models (Balcan et al., 2009).

In general, it is apparent that stochastic approaches have only recently been used to model influenza in humans. However, since the paper by Longini et al. (2004) this has been an increasingly important trend (Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Wu et al., 2006, van den Dool et al., 2008, Basta et al., 2009, Gojovic et al., 2009, Yang et al., 2009, Yasuda and Suzuki, 2009, Chao et al., 2010, Lee et al., 2010a, Tsai et al., 2010). Stochastic approaches have some advantage over deterministic models, primarily through the incorporation of more flexible methods to represent variability and uncertainty. The introduction of a disease may or may not necessarily lead to epidemic outbreak under similar condition based on chance alone.

This is particularly relevant in situations where numbers of infectious individuals and susceptible populations are small, when the infectious agent is not highly infectious, where spread occurs over smaller areas or where control measures are effectively implemented early in an outbreak (Roberts et al., 2007, Britton and Lindenstrand, 2009, Keeling and Danon, 2009, Lunelli et al., 2009). Furthermore, Britton & Lindenstrand (2009) demonstrated that the risk of a major outbreak is heavily dependent on the variability of the duration of the infectious period but not the latent period, whereas the initial growth rate of an influenza epidemic is greatly influenced by randomness in both periods. It is therefore likely that adopting a model which has limited capacity to capture stochastic behavior will, under these conditions, result in unrealistic predictions.

In general, most recent studies of pandemic influenza in humans have structured population by age, community (schools and daycare, workplace, households, etc.) and in some cases into high-risk and low-risk groups, using both deterministic and stochastic compartmental models (Brauer, 2008, Fraser et al., 2009, Gojovic et al., 2009, Milne et al., 2009, Ohkusa and Sugawara, 2009, Tuite et al., 2009, Lee et al., 2010b). Deterministic models with heterogeneous mixing which stratified populations into different subgroups were considered a balanced approach, as they are more realistic than homogeneous mixing, while remaining more efficient than stochastic, individual-based models in terms of simulation time and complexity (Eichner et al., 2007, Brauer, 2008). More complex and realistic models used to simulate influenza spread and evaluate intervention strategies included stochastic individual-based models (22 of the 93

articles), network models (8 articles), or spatially explicit agent-based and network models (3 articles). Some examples of these models include: individual-based models (Basta et al., 2009, Carpenter and Sattenspiel, 2009, Yang et al., 2009, Yasuda and Suzuki, 2009, Chao et al., 2010, Lee et al., 2010b, Perlroth et al., 2010, Tsai et al., 2010) , stochastic network models (Ajelli and Merler, 2008, Davey and Glass, 2008, Chao et al., 2010, Hsu and Shih, 2010, Perlroth et al., 2010), spatially explicit agent-based or network models (Ferguson et al., 2005, Longini et al., 2005, Halloran et al., 2008). The importance of incorporating spatial components in disease modeling were recognized both for evaluating spread and assessing the effect of control measures in humans (Ferguson et al., 2005, Halloran et al., 2008, Colizza et al., 2009, Lunelli et al., 2009) and in birds (Le Menach et al., 2006, Savill et al., 2006, Sharkey et al., 2008) as disease tended to spread more within localized areas. These models were considered to better represent real world conditions by capturing individual level behavior, heterogeneity in contact structure and hence the ability to capture phenomena such as super-spreading. In addition, these modeling approaches allow more flexibility in assessment of targeted intervention measures (e.g. towards high-risk individuals or groups) and policy planning. While these models add more realism, they have disadvantages in terms of computational efficiency, requiring long hours of simulation to assess a plausible range of parameter values (particularly if population size is large). They also tend to require parameter specification at a finer level of resolution and detail (e.g. individual-level contact structures, individual-level or age specific transmission parameters, etc.). In

addition, carrying out sensitivity analysis can be challenging since isolating influential parameters is difficult in the context of a large number of interacting parameters (Brauer, 2008, Gojovic et al., 2009). Therefore, it has been argued that simple deterministic compartmental models with heterogeneous mixing, which are also much easier to implement, represent a better alternative to these complex approaches for assessing disease management strategies during the early phase of an outbreak, particularly when little is known about model parameters (Chowell et al., 2006b, Eichner et al., 2007, Nuño et al., 2007a, Brauer, 2008). The qualitative results using simpler models for evaluating influenza control measures such as social distancing, antiviral treatment or vaccination (Nuño et al., 2007a) can be shown to be similar to those resulting from the creation of more complex models (Longini et al., 2004, Ferguson et al., 2005, Longini and Halloran, 2005, Longini et al., 2005, Ferguson et al., 2006, Germann et al., 2006). The choice of the most appropriate model: deterministic versus stochastic; compartmental versus individual-based; etc.; will depend on the nature of the agent or disease, the purpose of the research, the availability of parameters and the time-frame within which guidance is required (Nuño et al., 2007a, Brauer, 2008, Britton and Lindenstrand, 2009). A complete list of articles that used each of these different types of modeling approaches is provided in Table S1.

Only a few studies have investigated the spread of influenza at the household level using either deterministic or stochastic heterogeneous mixing compartmental models (Cauchemez et al., 2004, Fraser, 2007, Shaban et al., 2009), or a stochastic individual-

based model (Wu et al., 2006). These studies investigated the spread of influenza within and between households through contacts between infected and susceptible individuals locally (within household) and globally (between households). They also evaluated the effects of various intervention measures. This approach to modeling the spread of influenza at household level is analogous to disease spread at farm or herd level in animal populations, which often includes an assessment of similar intervention strategies (vaccination, quarantine, isolation, etc.). Modeling influenza spread at household and farm levels may be one approach for modeling the spread of influenza amongst and between animal and human populations that can effectively address different requirements in terms of model granularity.

2.4.2.2 Animals

There were 11 articles relating to studies that modeled influenza spread in birds. However, no papers reported the modeling of zoonotic influenza in swine or other animals (excluding one study of influenza viruses in equine populations (Garner et al., 2011), for which zoonotic importance is not yet known). Of the 11 avian articles, 6 assessed intervention strategies either alone or in combination with other questions of interests, 2 estimated parameters (van der Goot et al., 2003, Arinaminpathy and McLean, 2009), and 3 articles assessed the spread of avian influenza viruses (Bos et al., 2007, Guberti et al., 2007, Bavinck et al., 2009). Different types of models were adopted to address these questions in bird populations as summarized in Figure 2.1 and Table S1. These included simple deterministic compartmental models (Bos et al., 2007, Guberti et

al., 2007, Elbakidze, 2008, Arinaminpathy and McLean, 2009, Iwami et al., 2009), stochastic compartmental models (van der Goot et al., 2003, van der Goot et al., 2005, Bavinck et al., 2009), and a stochastic individual-based model (Savill et al., 2006). In addition, more complex models such as a deterministic network model (Aparicio and Pascual, 2007), a stochastic spatially explicit agent-based model (Le Menach et al., 2006), and a stochastic spatially explicit network (Sharkey et al., 2008) model for avian influenza viruses H5N1 and H7N7 were also used.

2.4.2.3 Multispecies zoonotic models

A key focus of this review was to characterize the literature related to modeling for multi-species zoonotic influenza spread. This review could identify only five articles relating to such modeling studies (Saenz et al., 2006, Arino et al., 2007, Iwami et al., 2007, Rao et al., 2009, Kim et al., 2010). Of these, one focused on methods and platform development to model the spread of avian influenza (A/H5N1 virus) from wild migratory water birds to domestic birds and humans as a function of spatially overlapping population densities (derived from spherical geometry based on great-circle distances to elicit interactions amongst water birds, poultry and humans) using an SIR model with Markov processes. Specifically designed software called SEARUMS (Studying the Epidemiology of Avian Influenza Rapidly Using Modeling and Simulation) was developed to facilitate this modeling (Rao et al., 2009). Another study investigated the spread of low pathogenic avian influenza (with the assumption that the virus mutated to become a pandemic virus) from birds to human and assessed the effect

of quarantine in both species using deterministic metapopulation modeling (Arino et al., 2007). Two studies used deterministic mathematical models to examine the mechanisms of spread of avian influenza from birds to humans (Iwami et al., 2007, Kim et al., 2010). They examined at what Ro values and contact rates the disease would be maintained or undergo extinction in bird and human populations, assuming a mutant form of the AI virus capable of human to human transmission emerged. All these studies assumed there was no back-transmission of influenza virus from humans to birds.

Only one study investigated the spread of novel influenza virus between humans and swine species in a rural setting, using a simple deterministic model with homogenous mixing (Saenz et al., 2006). It investigated the amplifying effect on epidemic size of influenza spread in confined animal feeding operations (CAFO) and transmission back to humans through CAFO workers. It was assumed that transmission of the influenza virus between CAFO species and the general community occurred only through CAFO workers. This study showed that human influenza cases would increase by 42–86% assuming that swine workers comprised between 15–45% of a given community, while vaccination of 50% of the CAFO workers effectively nullified any amplification. This study provided good preliminary insights into the effect of influenza spread between CAFO species and workers in a local setting. It would be worthwhile to apply more advanced modeling methods to assess other control strategies such as the effectiveness of biosecurity, impacts of early detection and control measures, contact reduction

between sick CAFO workers and swine, and a reduction in transmission probability through personal hygiene measures.

Another study assessed the exposure risk of susceptible domestic species to pandemic influenza A/H1N1 2009 upon its successful introduction into various populations in Vietnam (Boni et al., 2009). This study investigated the spread of pH1N1 2009 in humans by developing an age-structured gravity model and tracked the number of livestock owners (rearing swine and poultry) and non-livestock owners infected. From the number of livestock owners infected, they estimated the number of livestock exposed to the pandemic virus indirectly.

In terms of building a 'one-health' model to simulate spread of zoonotic influenza between animals and humans it is apparent that the most important differences relate to the unit of simulation as well as to the spatial and temporal scales involved. For humans, the unit of simulation is most often the individual. Individuals were assigned to spend differing amounts of time in various locations, such as at school, workplace or home, and disease spread was simulated in either continuous time-steps (Gani et al., 2005, Duerr et al., 2007, Nuño et al., 2007b, Brauer, 2008) or using two to four time-steps per day (Carrat et al., 2006, Ferguson et al., 2006, Ajelli and Merler, 2008, van den Dool et al., 2008, Basta et al., 2009). In animal populations the unit of simulation was mostly the farm, typically modeled in time-steps of one day (Le Menach et al., 2006, Guberti et al., 2007, Bavinck et al., 2009). Despite these differences, it seems feasible to simulate the spread of influenza between human and animal populations by adopting a relatively

simple approach which models at the household level. The household level model can be justified on the basis that it is pragmatic to implement most intervention measures such as antiviral drugs, vaccination, quarantine or isolation at the household level.

2.4.3 Intervention strategies

2.4.3.1 Humans

In general, the intervention strategies evaluated against pandemic influenza included: antiviral drugs for both prophylaxis and treatment of cases; vaccination; school, daycare and work place closure; personal hygiene; and other social distancing measures such as quarantine, isolation and travel restriction. These measures were evaluated either singly or in combination. A total of 63 articles evaluated different intervention strategies to control influenza in humans. The intervention evaluated most frequently was vaccination, either alone (14 articles) or in combination with other intervention measures (22 articles). This was followed by antivirals, either alone (6 articles) or in combination (30 articles). Eight articles evaluated social distancing measures, including one which specifically evaluated different strategies of school closure, such as isolating only sick students, closing individual schools or whole school system closures (Lee et al., 2010a). Four articles evaluated travel bans solely and five more studied travel ban in combination with other interventions as a means of controlling an influenza pandemic. This included three that specifically evaluated the effect of air travel restrictions in mitigating a pandemic. They observed that unless air travels restriction were imposed in approximately 100% of the affected countries, there would be no effect on influenza

spread, even though these measures delayed the peak of the influenza epidemic to varying degrees (Cooper et al., 2006, Hollingsworth et al., 2006, Wood et al., 2007). One article studied the effect of travel restriction between neighboring communities during a pandemic with similar results (Nigmatulina and Larson, 2009). The various types of models applied in the evaluation of these intervention measures are summarized in Figure 2.2. The two articles that assessed the effect of targeted antiviral prophylaxis and quarantine on containing a pandemic at source of origin, taking southeast Asia as the example case, were also the most highly cited references in the case of pandemic influenza modeling in human population (Longini et al., 2004, Ferguson et al., 2005).

All interventions using prophylactic antiviral treatment, vaccination or social distancing (such as quarantine and isolation) were evaluated based on the assumption that these measures were implemented at household, school or health care settings (Longini et al., 2004, Longini et al., 2005, Wu et al., 2006, Vardavas et al., 2007, van den Dool et al., 2008, Ander Heiden et al., 2009, Shaban et al., 2009, Lee et al., 2010b). It was difficult to compare the results of these studies as they evaluated the intervention measures under varying assumptions and population settings. However, all of these measures produced a positive effect on the containment of any influenza pandemic when implemented either singly or in combination with others.

The effects of these interventions were assessed by parameterizing the models through percentage reduction in contact rates (in the cases of social distancing measures such as school or workplace closure, or quarantine measures, etc.) and reduction in

susceptibility to infection and infectivity or duration of infectiousness (in the cases of antiviral treatment and vaccination). Parameters used in assessing these intervention measures are described in the "modeling parameters" section below. In general, the outcome of these models were assessed in terms of clinical attack rates, secondary attack rates, hospitalization rates, case fatality rates, duration of epidemic, and day to epidemic peak.

2.4.3.2 Birds

Five articles investigated intervention strategies for influenza in birds. They included movement control, quarantine, isolation, depopulation (Le Menach et al., 2006, Elbakidze, 2008, Sharkey et al., 2008), and vaccination (Savill et al., 2006, Iwami et al., 2009) against avian influenza A/H5N1 and H7N7. Outcomes of these models were assessed in terms of R_0 values, size of epidemic (number of infected premises), numbers depopulated and duration of epidemic.

2.4.3.3 Multispecies zoonoses

Two articles evaluated the effect of intervention measures on zoonotic spread. One considered the effect of vaccinating certain high-risk populations (50% of CAFO workers) against a novel influenza virus (Saenz et al., 2006), while the other examined the effect of quarantine measures on the spread of low pathogenic avian influenza in birds and humans (Arino et al., 2007).

2.4.4 Modeling software/platforms

The main purpose of this section is to provide an inventory of the software used for modeling rather than to describe features of each of these tools, which is beyond the scope of this review. Only 13 articles specified the modeling software or platform used; details are given in Table 2.1. Four modeling software were described fully for modeling influenza in humans. FluTe is a stochastic individual-based modeling platform capable of simulating large-scale spread of influenza and evaluation of intervention measures against pandemic influenza across major metropolitan areas or the continental US (Chao et al., 2010). InfluSim is a simple deterministic SEIR compartmental model that captures heterogeneous mixing (Eichner et al., 2007), while EpiFlex is a stochastic individual-based model which can simulate other diseases such as HIV and smallpox in addition to influenza (Hanley, 2006). Pandemic Influenza Policy Model (PIPM) is an agent-based model specifically designed for military settings (Feighner et al., 2009). All these modeling platforms can handle populations partitioned by demographic and clinical parameters and are available freely. Other modeling platforms mentioned in the literature were AnyLogic (two articles), Berkely Madonna, MATLAB, and RePAST (Recursive Porous Agent Simulation Toolkit), all of which are generic modeling platforms. Finally, GLEaM (Global Epidemic and Mobility Modeler), a stochastic metapopulation modeling platform for simulating large-scale spread of influenza viruses, was noted in one article (Balcan et al., 2009).

2.4.5 Modeling parameters

Parameters used in models related to the natural history of influenza viruses, contact and transmission parameters, as well as intervention measures are summarized in Table 2.2 to 2.15. Detailed lists of references from which these parameters were extracted are presented in Tables S3 to S6.

2.4.5.1 Natural history

Parameters associated with the natural history of influenza infection include those used to model: incubation, latency, subclinical (asymptomatic infectious), clinically infectious, and immune, periods. These parameters are presented according to influenza strains reported in the literature for humans in Table 2.2 to 2.3, and for birds and swine in Table 2.4 and 2.5. In addition, percentages of pre-existing immunity used in some of these studies for humans are presented under the natural history of influenza section in Table 2.3.

Parameters relating to disease state duration for different influenza viruses in humans were similar. Apparently modeling studies conducted after 2005 and prior to the pH1N1 2009 outbreaks (Flahault et al., 2006, Colizza et al., 2007, Duerr et al., 2007, Fraser, 2007, Halloran et al., 2008, Basta et al., 2009, Carpenter and Sattenspiel, 2009, Gojovic et al., 2009) mainly adopted the parameters (disease states durations, transmission parameters, contact frequencies and probabilities) specified in Ferguson et al. (2005, 2006), German et al. (2006), Longini et al. (2004, 2005) and Mills et al. (2004). Articles published after the outbreaks of pH1N1 2009 (Yang et al., 2009, Lee et al., 2010b,

Perlroth et al., 2010, Tuite et al., 2010) tended to use parameters from Boëlle et al. (2009), Fraser et al. (2009), and Pourbohloul et al. (2009). Distributional characteristics of parameters used for the natural history of influenza infection in humans and birds are presented in Table 2.6. The most commonly used distributions for incubation and latency period in human studies was a mean of 1.9 days with empirical distribution of one day (30%), 2 days (50%) and 3 days (20%) (Longini et al., 2004, Longini et al., 2005, Germann et al., 2006, Colizza et al., 2007, Ohkusa and Sugawara, 2007, Chao et al., 2010, Tsai et al., 2010), and the clinically infectious period with a mean of 4.1 days with empirical distribution of 3 days (30%), 4 days (40%), 5 days (20%) and 6 days (10%) (Halloran et al., 2002, Longini et al., 2004, Longini et al., 2005, Weycker et al., 2005, Germann et al., 2006, Ohkusa and Sugawara, 2009, Tsai et al., 2010). No study estimated the duration of disease state parameters for any influenza virus at the household level in humans (which would be required if spread of influenza were to be modeled at the household level). None of the articles included in this review provided information on distributions related to the natural history of influenza infection in swine.

2.4.5.2 Contact parameters

Daily contact frequencies for different age groups, household sizes, student groups, risk behaviors (highly active or less active subgroups of a population), and different community structures are summarized in Table 2.7. Parameters relating to contact frequencies used for modeling in human populations were either derived from small pilot surveys (Longini et al., 2005, Yang et al., 2009, Yasuda and Suzuki, 2009, Lee et

al., 2010a) or from a large-scale survey carried out in eight European countries (Mossong et al., 2008, Hens et al., 2009). These contact frequencies were defined as adequate contact (sufficient to transmit influenza virus between infectious and susceptible individuals) of a physical nature such as skin-to-skin contact, kiss or handshake, or a two-way conversation consisting of three or more words. Although, the latter two articles used the same survey data, there were minor differences in the way contact frequencies were estimated, in particular, number of contacts at works were included in the article by Hens et al. (2009). A number of recently published articles (Medlock and Meyers, 2009, Tuite et al., 2009, Chao et al., 2010, Tuite et al., 2010) used the contact frequencies estimated by Mossong et al. (2008). Estimates of daily contact frequencies used in other articles are summarized separately in Table 2.7. Both direct and indirect contact rates between poultry or poultry farms, extracted from two articles (Elbakidze, 2008, Sharkey et al., 2008), are also summarized in Table 2.7.

2.4.5.3 Transmission parameters

Transmission parameters in disease spread models use either R_0 in combination with a generation interval, or a transmission coefficient derived by multiplying contact frequency and transmission probability per contact and duration of relevant disease states. Some models used a single value of β defined as the per capita rate at which two individuals come into effective contact (i.e. adequate contact that will lead to infection if one is infectious and other is susceptible) (Vynnycky and White, 2010) . Not all adequate contact will be effective (e.g. an adequate contact between infectious

individual and immune individual will not be effective contact). Transmission probability per adequate contact (including contact frequencies) or transmission coefficient/contact rates (without requiring knowledge of contact frequency) were all estimated by calibrating these to match the attack rates (proportion of newly infected individuals in a exposed population) or R_0 values of past influenza pandemics (pandemic influenza A/H1N1 1918-1919, influenza A/H2N2 1957-58, and influenza A/H3N2 1968-1969). Transmission probabilities were estimated using varying units of contact frequency, such as frequency per day (Longini et al., 2005, Chao et al., 2010), frequency per hour (Gojovic et al., 2009), contact duration expressed in minutes per day (Lee et al., 2010a), or as a probability per simulation time-step (Viboud et al., 2004). The transmission probabilities presented in Table 2.8 are a summary of all these estimates. Transmission probabilities for within-flock bird to bird and per dangerous contact through trucks picking up birds for slaughterhouse are also presented in Table 2.8.

Similarly transmission coefficients/rates were expressed in units of continuous time, per-day or certain hours/day. Transmission coefficients/rates which were expressed in terms of daily or 8 to 12 hourly intervals were summarized together, whereas those expressed in continuous time unit from seconds to hourly intervals were summarized separately and are presented in Table 2.9. Assumed values of transmission coefficient/rates for between-species transmission of influenza are also presented in the same table. Since these transmission probabilities and coefficients were calibrated under different disease spread scenarios and other assumptions, they are intended only to

provide readers with an overview of the ranges of values used. In addition, all these parameters were summarized over all contact types. For more detailed information relating to specific contact patterns and transmission probabilities, readers may refer the original articles.

Estimates of mean R_0 values, with and without 95% confidence intervals, for different influenza viruses in different human populations are presented in Tables 2.10 and 11 respectively. Reproductive numbers based either on references from other literature or assumed within the reported models in human population are also presented in Table 2.11. Chowell et al. (2006a) and (2007a) have estimated ranges of R_0 values for pandemic influenza A/H1N1 1918 based on different datasets collected around spring and autumn waves of outbreaks in Geneva, Switzerland. Autumn outbreaks had significantly higher R_0 values than spring waves. They also estimated R_0 values based on a different set of outbreak data from San Francisco, California, and by applying different modeling methods with some differences in the estimates. Estimates of R_0 values for the most recent pH1N1 2009 virus were reported in Pourbohloul et al., (2009), Tuite et al., (2010) and using four different approaches by Boëlle et al., (2009). The estimates from the first two studies were significantly lower compared with those of Boëlle et al., (2009). In general, R_0 values for all pandemic influenza outbreaks ranged from 1.1 to 4.0. Two articles estimated R_0 values for influenza spread at the household level (Fraser, 2007, Shaban et al., 2009). The effect of household size on the basic reproductive number was evaluated by taking examples of small and large household

size distributions for populations in Sweden and Tanzania respectively (Shaban et al., (2009). This study found that the R_0 for between-household spread was much higher in populations with larger family size ($R_0 = 6$) than in those with smaller family size ($R_0 = 2$).

Basic reproductive numbers estimated with 95% CI for different influenza viruses in birds at individual and flock levels are presented in Table 2.12. Summary of R_0 estimated (without 95% CI), referenced and assumed at the individual, flock and village levels in the literature are summarized in Table 2.13. Different R_0 values assumed for different species in modeling zoonotic transmission of novel influenza virus between human and swine or birds are also presented in Table 2.13.

Summary estimates of generation intervals or serial intervals (time from onset of primary case to a secondary case (Vynnycky and White, 2010)) are presented in Table 2.14. Generation intervals are estimated by adding the averages of incubation or latency period and infectious period stated in the models.

2.4.5.4 Parameters for intervention measures

Parameters used for assessing different intervention strategies in human and bird populations are presented in Table 2.15. The estimated efficacy of antiviral treatment ranged from 61–90% (Hayden and Aoki, 1999, Lipsitch et al., 2003), whereas efficacy values used for modeling ranged from 28–100%. Reduction in infectivity by infected person through treatment used for modeling ranged from 28–100%, and for susceptibility through prophylactic treatment from 25–100%. The antiviral coverage

rate, treatment duration including compliance rate are provided in the same table. The estimated vaccine efficacy for influenza in human ranged from 19–68% (Vu et al., 2002, Hayden et al., 2004). However, its values used (referenced or assumed values) in the models ranged from, 5–100%. Reduction in infectiousness by infected person due to vaccination used in the models ranged from 20–100% with a delay to immunity from no delay to 15–42 days. The vaccination coverage evaluated ranged from 18–100% in humans.

Assessment of school and day-care closure were modeled through contact reduction ranging from 30–100% with the closure period ranging from 7–300 days. The delay to school closure from the first case ranged from without any delay to 7–56 days. The values used for reduction in contacts as a result of quarantine or isolation in human populations ranged from 40-100% while the duration of quarantine or isolation periods ranged from 1–21 days. A quarantine period of 21–31 days with 100% effectiveness was assumed for infected bird flocks (Sharkey et al., 2008).

It was apparent that there is adequate information on disease states and transmission parameters to model spread of influenza viruses in human population, including the recently emerged pH1N1 virus. While some data exist for influenza viruses in birds, very little information on parameters other than disease state duration (Brookes et al., 2010, Pasma and Joseph, 2010, Vincent et al., 2010) exists for swine influenza viruses (including the pH1N1 virus) for the review period considered; despite the fact that many outbreaks in swine have been reported from a range of countries (OIE, 2009-2010) .

2.5 Conclusion

This study has provided a synopsis of the different methods and approaches applied to modeling the spread of zoonotic influenza in humans and animal populations, including a summary of important modeling parameters. It was apparent that the majority of recent influenza modeling studies applied to human populations had been motivated by the perceived threat of the emergence of a mutant strain of the avian influenza A/H5N1 and pH1N1 viruses. However, only four studies modeled the transmission dynamic of influenza spread between birds and humans, and one study modeled its spread at swine-humans interface. In spite of the recognized role of swine as a potential mixing host for different influenza viruses (particularly avian and human influenza viruses) in generating novel viruses through reassortment, and considering the fact that the pH1N1 virus is known to readily transmit between swine and humans, modeling research at the animal-human interface has been relatively sparse. Significant gaps in the knowledge of parameters such as frequency of evolution of novel viral strains in pigs, farm-level natural history of influenza infection in swine, incidences of its transmission between farms, and between pigs and humans are clearly evident. Given the potential benefits of simulation studies not only for understanding the transmission dynamics of zoonotic influenza but also in investigating various scenarios for contingency planning and developing sound early warning systems, it seems clear that priority must be given to research at the animal-human interface. This is imperative bearing in mind the continued threat posed by the repeated emergence of pandemic influenza viruses and the potential

role animals may play in generating novel influenza viruses. It was also evident that there are adequate numbers of both generic and specific software (both for commercial and free) available for modeling influenza spread in human and animal populations using methods ranging from a simple deterministic to a more complex and realistic network-based models.

2.6 References

Addy, C. L., I. M. Longini, Jr. and M. Haber, 1991: A generalized stochastic model for the analysis of infectious disease final size data. Biometrics, 47, 961-974.

Ajelli, M. and S. Merler, 2008: The impact of the unstructured contacts component in influenza pandemic modeling. PLoS One 3, e1519.

Ander Heiden, M., U. Buchholz, G. Krause, G. Kirchner, H. Claus and W. H. Haas, 2009: Breaking the waves: modelling the potential impact of public health measures to defer the epidemic peak of novel influenza A/H1N1. PLoS One, 4, e8356.

Aparicio, J. P. and M. Pascual, 2007: Building epidemiological models from R0: an implicit treatment of transmission in networks. Proc. R. Soc. Lond. B. Biol. Sci., 274, 505-512.

Arinaminpathy, N. and A. R. McLean, 2008: Antiviral treatment for the control of pandemic influenza: some logistical constraints. J. R. Soc. Interface, 5, 545-553.

Arinaminpathy, N. and A. R. McLean, 2009: Evolution and emergence of novel human infections. Proc. Biol. Sci., 276, 3937-3943.

Arino, J., F. Brauer, P. van den Driessche, J. Watmough and J. Wu, 2008: A model for influenza with vaccination and antiviral treatment. J. Theor. Biol., 253, 118-130.

Arino, J., R. Jordan and P. van den Driessche, 2007: Quarantine in a multi-species epidemic model with spatial dynamics. Math. Biosci., 206, 46-60.

Balcan, D., V. Colizza, B. Gonçalves, H. Hu, J. J. Ramasco and A. Vespignani, 2009: Multiscale mobility networks and the spatial spreading of infectious diseases. Proc. Natl. Acad. Sci. U. S. A., 106, 21484-21489.

Basta, N. E., D. L. Chao, M. E. Halloran, L. Matrajt and I. M. Longini, Jr., 2009: Strategies for pandemic and seasonal influenza vaccination of schoolchildren in the United States. Am. J. Epidemiol., 170, 679-686.

Bavinck, V., A. Bouma, M. van Boven, M. E. H. Bos, E. Stassen and J. A. Stegeman, 2009: The role of backyard poultry flocks in the epidemic of highly pathogenic avian influenza virus (H7N7) in the Netherlands in 2003. Prev. Vet. Med., 88, 247-254.

Boëlle, P. Y., P. Bernillon and J. C. Desenclos, 2009: A preliminary estimation of the reproduction ratio for new influenza A(H1N1) from the outbreak in Mexico, March-April 2009. Euro Surveill, 14, pii=19205.

Boni, M. F., B. H. Manh, P. Q. Thai, J. Farrar, T. T. Hien, N. T. Hien, N. Van Kinh and P. Horby, 2009: Modelling the progression of pandemic influenza A (H1N1) in

Vietnam and the opportunities for reassortment with other influenza viruses. BMC. Med., 7, 43.

Bos, M. E. H., M. v. Boven, M. Nielen, A. Bouma, A. R. W. Elbers, G. Nodelijk, G. Koch, A. Stegeman and M. C. M. d. Jong, 2007: Estimating the day of highly pathogenic avian influenza (H7N7) virus introduction into a poultry flock based on mortality data. Vet. Res., 38, 493-504.

Brauer, F., 2008: Epidemic models with heterogeneous mixing and treatment. Bull. Math. Biol., 70, 1869-1885.

Britton, T. and D. Lindenstrand, 2009: Epidemic modelling: Aspects where stochasticity matters. Math. Biosci., 222, 109-116.

Brookes, S. M., A. Nunez, B. Choudhury, M. Matrosovich, S. C. Essen, D. Clifford, M. J. Slomka, G. Kuntz-Simon, F. Garcon, B. Nash, A. Hanna, P. M. Heegaard, S. Queguiner, C. Chiapponi, M. Bublot, J. M. Garcia, R. Gardner, E. Foni, W. Loeffen, L. Larsen, K. Van Reeth, J. Banks, R. M. Irvine and I. H. Brown, 2010: Replication, pathogenesis and transmission of pandemic (H1N1) 2009 virus in non-immune pigs. PLoS One, 5, e9068. doi:9010.1371/journal.pone.0009068.

Brown, I. H., 2000: The epidemiology and evolution of influenza viruses in pigs. Vet. Microbiol., 74, 29-46.

Carpenter, C. and L. Sattenspiel, 2009: The design and use of an agent-based model to simulate the 1918 influenza epidemic at Norway House, Manitoba. Am. J. Hum. Biol., 21, 290-300.

Carrat, F., J. Luong, H. Lao, A. V. Salle, C. Lajaunie and H. Wackernagel, 2006: A 'small-world-like' model for comparing interventions aimed at preventing and controlling influenza pandemics. BMC. Med., 4, 1-14.

Carrat, F., E. Vergu, N. M. Ferguson, M. Lemaitre, S. Cauchemez, S. Leach and A. J. Valleron, 2008: Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am. J. Epidemiol., 167, 775-785.

Cauchemez, S., F. Carrat, C. Viboud, A. J. Valleron and P. Y. Boelle, 2004: A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. Stat. Med., 23, 3469-3487.

Chao, D. L., M. E. Halloran, V. J. Obenchain and I. M. Longini, 2010: FluTE, a Publicly Available Stochastic Influenza Epidemic Simulation Model. PLoS Comput. Biol., 6, e1000656.

Chen, S.-C. and C.-M. Liao, 2010: Probabilistic indoor transmission modeling for influenza (sub)type viruses. J. Infect., 60, 26-35.

Chowell, G., C. E. Ammon, N. W. Hengartner and J. M. Hyman, 2006a: Estimation of the reproductive number of the Spanish flu epidemic in Geneva, Switzerland. Vaccine, 24, 6747-6750.

Chowell, G., C. E. Ammon, N. W. Hengartner and J. M. Hyman, 2006b: Transmission dynamics of the great influenza pandemic of 1918 in Geneva, Switzerland: Assessing the effects of hypothetical interventions. J. Theor. Biol., 241, 193-204.

Chowell, G., C. E. Ammon, N. W. Hengartner and J. M. Hyman, 2007a: Estimating the reproduction number from the initial phase of the Spanish flu pandemic waves in Geneva, Switzerland. Math. Biosci. Eng., 4, 457-470.

Chowell, G., L. M. Bettencourt, N. Johnson, W. J. Alonso and C. Viboud, 2008a: The 1918-1919 influenza pandemic in England and Wales: spatial patterns in transmissibility and mortality impact. Proc. Biol. Sci., 275, 501-509.

Chowell, G., M. A. Miller and C. Viboud, 2008b: Seasonal influenza in the United States, France, and Australia: transmission and prospects for control. Epidemiol. Infect., 136, 852-864.

Chowell, G. and H. Nishiura, 2008: Quantifying the transmission potential of pandemic influenza. Phys. Life. Rev., 5, 50-77.

Chowell, G., H. Nishiura and L. M. Bettencourt, 2007b: Comparative estimation of the reproduction number for pandemic influenza from daily case notification data. J. R. Soc. Interface, 4, 155-166.

Colizza, V., A. Barrat, M. Barthelemy, A. J. Valleron and A. Vespignani, 2007: Modeling the worldwide spread of pandemic influenza: baseline case and containment interventions. PLoS Med., 4, e13-e13.

Colizza, V., A. Vespignani, N. Perra, C. Poletto, B. Goncalves, H. Hu, D. Balcan, D. Paolotti, W. Van den Broeck, M. Tizzoni, P. Bajardi and J. J. Ramasco, 2009: Estimate of Novel Influenza A/H1N1 cases in Mexico at the early stage of the pandemic with a spatially structured epidemic model. PLoS Curr. Influenza., RRN1129.

Cooper, B. S., R. J. Pitman, W. J. Edmunds and N. J. Gay, 2006: Delaying the international spread of pandemic influenza. PLoS Med., 3, e212-e212.

Cowling, B. J., V. J. Fang, S. Riley, J. S. M. Peiris and G. M. Leung, 2009: Estimation of the serial interval of influenza. Epidemiology, 20, 344-347.

Das, T., A. Savachkin and Y. Zhu, 2008: A large-scale simulation model of pandemic influenza outbreaks for development of dynamic mitigation strategies. IIE Trans., 40, 893-905.

Davey, V. J. and R. J. Glass, 2008: Rescinding community mitigation strategies in an influenza pandemic. Emerg. Infect. Dis., 14, 365-372.

Davey, V. J., R. J. Glass, H. J. Min, W. E. Beyeler and L. M. Glass, 2008: Effective, robust design of community mitigation for pandemic influenza: a systematic examination of proposed US guidance. PLoS One, 3, e2606.

Dohoo, I., W. Martin and H. Stryhn, 2009: Veterinary epidemiologic research, 2 edn. VER Inc., Charlottetown, PEI, Canada.

Duerr, H. P., S. O. Brockmann, I. Piechotowski, M. Schwehm and M. Eichner, 2007: Influenza pandemic intervention planning using InfluSim: pharmaceutical and non-pharmaceutical interventions. BMC Infect. Dis., 7, 1-13.

Eichner, M., M. Schwehm, H. P. Duerr and S. O. Brockmann, 2007: The influenza pandemic preparedness planning tool InfluSim. BMC Infect. Dis., 7, 17.

Elbakidze, L., 2008: Modeling of avian influenza mitigation policies within the backyard segment of the poultry sector. J. Agr. Econ. Res., 33, 195-211.

Elveback, L. R., J. P. Fox, E. Ackerman, A. Langworthy, M. Boyd and L. Gatewood, 1976: An influenza simulation model for immunization studies. Am. J. Epidemiol., 103, 152-165.

Epstein, J. M., D. M. Goedecke, F. Yu, R. J. Morris, D. K. Wagener and G. V. Bobashev, 2007: Controlling pandemic flu: the value of international air travel restrictions. PLoS One, 2, e401.

Feighner, B. H., J. P. Chrétien , S. P. Murphy, J. F. Skora, J. S. Coberly, J. E. Dietz, J. L. Chaffee, M. L. Sikes, M. J. Mabee, B. P. Russell and J. C. Gaydos, 2009: The pandemic influenza policy model: a planning tool for military public health officials. Mil. Med., 174, 557-565.

Ferguson, N. M., D. A. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn and D. S. Burke, 2005: Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature, 437, 209-214.

Ferguson, N. M., D. A. T. Cummings, C. Fraser, J. C. Cajka, P. C. Cooley and D. S. Burke, 2006: Strategies for mitigating an influenza pandemic. Nature, 442, 448-452.

Ferguson, N. M., C. A. Donnelly and R. M. Anderson, 2001a: The foot-and-mouth epidemic in Great Britain: pattern of spread and impact of interventions. Science, 292, 1155-1160.

Ferguson, N. M., C. A. Donnelly and R. M. Anderson, 2001b: Transmission intensity and impact of control policies on the foot and mouth epidemic in Great Britain. Nature, 413, 542-548.

Fiore, A., D. Shay, K. Broder, J. Iskander, T. Uyeki, G. Mootrey, J. Bresee and N. Cox, 2008: Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR, 57, 1-60.

Flahault, A., S. Deguen and A. J. Valleron, 1994: A mathematical model for the European spread of influenza. Eur. J. Epidemiol., 10, 471-474.

Flahault, A., E. Vergu and P. Y. Boelle, 2009: Potential for a global dynamic of Influenza A (H1N1). BMC Infect. Dis., 9, 129.

Flahault, A., E. Vergu, L. Coudeville and R. F. Grais, 2006: Strategies for containing a global influenza pandemic. Vaccine, 24, 6751-6755.

Fraser, C., 2007: Estimating individual and household reproduction numbers in an emerging epidemic. PLoS One, 2, e758.

Fraser, C., C. A. Donnelly, S. Cauchemez, W. P. Hanage, M. D. Van Kerkhove, T. D. i. Hollingsworth, J. Griffin, R. F. Baggaley, H. E. Jenkins, E. J. Lyons, T. Jombart, W. R. Hinsley, N. C. Grassly, F. Balloux, A. C. Ghani, N. M. Ferguson, A. Rambaut, O. G. Pybus, H. Lopez-Gatell, C. M. Alpuche-Aranda, I. B. Chapela, E. P. Zavala, D. M. E. Guevara, F. Checchi, E. Garcia, S. Hugonnet and C. Roth, 2009: Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings. Science, 324, 1557-1561.

Gani, R., H. Hughes, D. Fleming, T. Griffin, J. Medlock and S. Leach, 2005: Potential impact of antiviral drug use during influenza pandemic. Emerg. Infect. Dis., 11, 1355-1362.

Garner, M. G., B. Cowled, I. J. East, B. J. Moloney and N. Y. Kung, 2011: Evaluating the effectiveness of early vaccination in the control and eradication of equine influenza—A modelling approach. Prev. Vet. Med., 99, 15-27.

Germann, T. C., K. Kadau, I. M. Longini, Jr. and C. A. Macken, 2006: Mitigation strategies for pandemic influenza in the United States. Proc. Natl. Acad. Sci. U. S. A., 103, 5935-5940.

Glass, K. and B. Barnes, 2007: How much would closing schools reduce transmission during an influenza pandemic? Epidemiology, 18, 623-628.

Gojovic, M. Z., B. Sander, D. Fisman, M. D. Krahn and C. T. Bauch, 2009: Modelling mitigation strategies for pandemic (H1N1) 2009. Can. Med. Assoc. J., 181, 673-680.

Grais, R. F., J. H. Ellis and G. E. Glass, 2003: Assessing the impact of airline travel on the geographic spread of pandemic influenza. Eur. J. Epidemiol., 18, 1065-1072.

Grais, R. F., J. H. Ellis, A. Kress and G. E. Glass, 2004: Modeling the spread of annual influenza epidemics in the U.S.: the potential role of air travel. Health Care Manag. Sci., 7, 127-134.

Guberti, V., M. Scremin, L. Busani, L. Bonfanti and C. Terregino, 2007: A simulation model for low-pathogenicity avian influenza viruses in dabbling ducks in Europe. Avian Dis., 51, 275-278.

Gumel, A. B., S. Ruan, T. Day, J. Watmough, F. Brauer, P. van den Driessche, D. Gabrielson, C. Bowman, M. E. Alexander, S. Ardal, J. Wu and B. M. Sahai, 2004: Modelling strategies for controlling SARS outbreaks. Proc. Biol. Sci., 271, 2223-2232.

Halloran, M. E., N. M. Ferguson, S. Eubank, I. M. Longini, Jr., D. A. T. Cummings, B. Lewis, S. Xu, C. Fraser, A. Vullikanti, T. C. Germann, D. Wagener, R. Beckman, K. Kadau, C. Barrett, C. A. Macken, D. S. Burke and P. Cooley, 2008: Modeling targeted layered containment of an influenza pandemic in the United States. Proc. Natl. Acad. Sci. U. S. A., 105, 4639-4644.

Halloran, M. E., I. M. Longini, D. M. Cowart and A. Nizam, 2002: Community interventions and the epidemic prevention potential. Vaccine, 20, 3254-3262.

Hanley, B., 2006: An object simulation model for modeling hypothetical disease epidemics - EpiFlex. Theor. Biol. Med. Model., 3, 32.

Harper, S., K. Fukuda, T. Uyeki, N. Cox and C. Bridges, 2004: Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR, 53, 1-40.

Hayden, F. G. and F. Y. Aoki, 1999: Amantadine, rimantadine, and related agents, antiviral agents. In: V. L. Yu, T. C. Merigan and S. L. Barriere (eds), Antimicrobial therapy and vaccines, eds. edn., pp. 1344-1365. Williams and Wilkins, Baltimore, MD. pp 1344-1365.

Hayden, F. G., R. Belshe, C. Villanueva, R. Lanno, C. Hughes, I. Small, R. Dutkowski, P. Ward and J. Carr, 2004: Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J. Infect. Dis., 189, 440-449.

Hens, N., N. Goeyvaerts, M. Aerts, Z. Shkedy, P. v. Damme and P. Beutels, 2009: Mining social mixing patterns for infectious disease models based on a two-day population survey in Belgium. BMC Infect. Dis., 9, 1-18.

Hollingsworth, T. D., N. M. Ferguson and R. M. Anderson, 2006: Will travel restrictions control the international spread of pandemic influenza? Nat. Med., 12, 497-499.

Howden, K. J., E. J. Brockhoff, F. D. Caya, L. J. McLeod, M. Lavoie, J. D. Ing, J. M. Bystrom, S. Alexandersen, J. M. Pasick, Y. Berhane, M. E. Morrison, J. M. Keenliside, S. Laurendeau and E. B. Rohonczy, 2009: An investigation into human pandemic influenza virus (H1N1) 2009 on an Alberta swine farm. Can. Vet. J., 50, 1153-1161.

Hsu, C.-I. and H.-H. Shih, 2010: Transmission and control of an emerging influenza pandemic in a small-world airline network. Accid. Anal. Prev., 42, 93-100.

Itoh, Y., K. Shinya, M. Kiso, T. Watanabe, Y. Sakoda, M. Hatta, Y. Muramoto, D. Tamura, Y. Sakai-Tagawa, T. Noda, S. Sakabe, M. Imai, Y. Hatta, S. Watanabe, C. Li, S. Yamada, K. Fujii, S. Murakami, H. Imai, S. Kakugawa, M. Ito, R. Takano, K. Iwatsuki-Horimoto, M. Shimojima, T. Horimoto, H. Goto, K. Takahashi, A. Makino, H. Ishigaki, M. Nakayama, M. Okamatsu, K. Takahashi, D. Warshauer, P. A. Shult, R. Saito, H. Suzuki, Y. Furuta, M. Yamashita, K. Mitamura, K. Nakano, M. Nakamura, R. Brockman-Schneider, H. Mitamura, M. Yamazaki, N. Sugaya, M. Suresh, M. Ozawa, G. Neumann, J. Gern, H. Kida, K. Ogasawara and Y. Kawaoka, 2009: In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. Nature; doi:10.1038/nature08260.

Iwami, S., T. Suzuki and Y. Takeuchi, 2009: Paradox of vaccination: is vaccination really effective against avian flu epidemics? PLoS One, 4, e4915.

Iwami, S., Y. Takeuchi and X. Liu, 2007: Avian-human influenza epidemic model. Math. Biosci., 207, 1-25.

Jones, K. E., N. G. Patel, M. A. Levy, A. Storeygard, D. Balk, J. L. Gittleman and P. Daszak, 2008: Global trends in emerging infectious diseases. Nature, 451, 990-993.

Keeling, M. and P. Rohani, 2008: Modeling Infectious Diseases in Humans and Animals. pp. 1-13, 15-52. Princeton University Press, Princeton, New Jersey.

Keeling, M. J. and L. Danon, 2009: Mathematical modelling of infectious diseases. Br. Med. Bull., 92, 33-42.

Keeling, M. J., M. E. Woolhouse, D. J. Shaw, L. Matthews, M. Chase-Topping, D. T. Haydon, S. J. Cornell, J. Kappey, J. Wilesmith and B. T. Grenfell, 2001: Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape. Science, 294, 813-817.

Kim, K. I., Z. Lin and L. Zhang, 2010: Avian-human influenza epidemic model with diffusion. Nonlinear Analysis: Real World Applications, 11, 313-322.

Lange, E., D. Kalthoff, U. Blohm, J. P. Teifke, A. Breithaupt, C. Maresch, E. Starick, S. Fereidouni, B. Hoffmann, T. C. Mettenleiter, M. Beer and T. W. Vahlenkamp, 2009: Pathogenesis and transmission of the novel swine-origin influenza virus A/H1N1 after experimental infection of pigs. J. Gen. Virol., 90, 2119-2123.

Larson, R. C., 2007: Simple Models of Influenza Progression Within a Heterogeneous Population. Oper. Res., 55, 399-412.

Lavenu, A., A. J. Valleron and F. Carrat, 2004: Exploring cross-protection between influenza strains by an epidemiological model. Virus Res., 103, 101-105.

Le Menach, A., E. Vergu, R. F. Grais, D. L. Smith and A. Flahault, 2006: Key strategies for reducing spread of avian influenza among commercial poultry holdings:

lessons for transmission to humans. Proc. R. Soc. Lond. B. Biol. Sci., 273, 2467-2475.

Lee, B. Y., S. T. Brown, P. Cooley, M. A. Potter, W. D. Wheaton, R. E. Voorhees, S. Stebbins, J. J. Grefenstette, S. M. Zimmer, R. K. Zimmerman, T. M. Assi, R. R. Bailey, D. K. Wagener and D. S. Burke, 2010a: Simulating school closure strategies to mitigate an influenza epidemic. J. Public Health Manag. Pract., 16, 252-261.

Lee, B. Y., S. T. Brown, P. C. Cooley, R. K. Zimmerman, W. D. Wheaton, S. M. Zimmer, J. J. Grefenstette, T. M. Assi, T. J. Furphy, D. K. Wagener and D. S. Burke, 2010b: A computer simulation of employee vaccination to mitigate an influenza epidemic. Am. J. Prev. Med., 38, 247-257.

Lessler, J., N. G. Reich, R. Brookmeyer, T. M. Perl, K. E. Nelson and D. A. T. Cummings, 2009: Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect. Dis., 9, 291-300.

Lindstrom, S., G. Rebecca, B. Amanda, S. Bo, E. Shannon, B. LaShondra, B. Nathelia, S. Katrina, G. Larisa, V. Julie and K. Alexander, 2012: Human Infections with Novel Reassortant Influenza A(H3N2)v Viruses, United States, 2011. Emerg. Infect. Dis., 18, 834-837.

Lipsitch, M., T. Cohen, B. Cooper, J. M. Robins, S. Ma, L. James, G. Gopalakrishna, S. K. Chew, C. C. Tan, M. H. Samore, D. Fisman and M. Murray, 2003: Transmission dynamics and control of severe acute respiratory syndrome. Science, 300, 1966-1970.

Lloyd-Smith, J. O., A. P. Galvani and W. M. Getz, 2003: Curtailing transmission of severe acute respiratory syndrome within a community and its hospital. Proc. Biol. Sci., 270, 1979-1989.

Lloyd-Smith, J. O., D. George, K. M. Pepin, V. E. Pitzer, J. R. Pulliam, A. P. Dobson, P. J. Hudson and B. T. Grenfell, 2009: Epidemic dynamics at the human-animal interface. Science, 326, 1362-1367.

Longini, I. M., Jr. and M. E. Halloran, 2005: Strategy for distribution of influenza vaccine to high-risk groups and children. Am. J. Epidemiol., 161, 303-306.

Longini, I. M., Jr., M. E. Halloran, A. Nizam and Y. Yang, 2004: Containing pandemic influenza with antiviral agents. Am. J. Epidemiol., 159, 623-633.

Longini, I. M., A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D. A. T. Cummings and M. E. Halloran, 2005: Containing Pandemic Influenza at the Source. Science, 309, 1083-1087.

Lunelli, A., A. Pugliese and C. Rizzo, 2009: Epidemic patch models applied to pandemic influenza: contact matrix, stochasticity, robustness of predictions. Math. Biosci., 220, 24-33.

Ma, W., K. M. Lager, A. L. Vincent, B. H. Janke, M. R. Gramer and J. A. Richt, 2009: The Role of Swine in the Generation of Novel Influenza Viruses. Zoonoses Public Health, 56, 326–337.

Massad, E., M. N. Burattini, F. A. Coutinho and L. F. Lopez, 2007: The 1918 influenza A epidemic in the city of Sao Paulo, Brazil. Med. Hypotheses, 68, 442-445.

Medlock, J. and L. A. Meyers, 2009: Optimizing allocation for a delayed influenza vaccination campaign. PLoS Curr. Influenza., RRN1134.

Meltzer, M. I., N. J. Cox and K. Fukuda, 1999: The economic impact of pandemic influenza in the United States: priorities for intervention. Emerg. Infect. Dis., 5, 659-671.

Mills, C. E., J. M. Robins and M. Lipsitch, 2004: Transmissibility of 1918 pandemic influenza. Nature, 432, 904-906.

Milne, G., J. Kelso and H. Kelly, 2009: Strategies for mitigating an influenza pandemic with pre-pandemic H5N1 vaccines. J. R. Soc. Interface.

Morris, R. S., J. W. Wilesmith, M. W. Stern, R. L. Sanson and M. A. Stevenson, 2001: Predictive spatial modelling of alternative control strategies for the foot-and-mouth disease epidemic in Great Britain, 2001. Vet. Rec., 149, 137-144.

Mossong, J., N. Hens, M. Jit, P. Beutels, K. Auranen, R. Mikolajczyk, M. Massari, S. Salmaso, G. S. Tomba, J. Wallinga, J. Heijne, M. Sadkowska-Todys, M. Rosinska and W. J. Edmunds, 2008: Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med., 5, e74-e74.

Nigmatulina, K. R. and R. C. Larson, 2009: Living with influenza: Impacts of government imposed and voluntarily selected interventions. European Journal of Operational Research, 195, 613-627.

Nuño, M., G. Chowell and A. B. Gumel, 2007a: Assessing the role of basic control measures, antivirals and vaccine in curtailing pandemic influenza: scenarios for the US, UK and the Netherlands. J. R. Soc. Interface, 4, 505-521.

Nuño, M., G. Chowell, X. Wang and C. Castillo-Chavez, 2007b: On the role of cross-immunity and vaccines on the survival of less fit flu-strains. Theor. Popul. Biol., 71, 20-29.

Nuño, M., T. A. Reichert, G. Chowell and A. B. Gumel, 2008: Protecting residential care facilities from pandemic influenza. Proc. Natl. Acad. Sci. U. S. A., 105, 10625-10630.

Ohkusa, Y. and T. Sugawara, 2007: Application of an individual-based model with real data for transportation mode and location to pandemic influenza. J. Infect. Chemother., 13, 380-389.

Ohkusa, Y. and T. Sugawara, 2009: Simulation model of pandemic influenza in the whole of Japan. Jpn. J. Infect. Dis., 62, 98-106.

OIE, 2009: World Animal Health Information Database Weekly Disease Information: A/H1N1 influenza, Canada (Immediate notification : 05/05/2009). Available at http://www.oie.int/wahis_2/public%5C..%5Ctemp%5Creports/en_imm_0000008065_20090505_191855.pdf (accessed 28 April 2010). Paris.

OIE, 2009-2010: World Animal Health Information Database Weekly Disease Information. Available at http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/reportarchive (accessed on 22 April 2010). Paris.

Pasma, T. and T. Joseph, 2010: Pandemic (H1N1) 2009 infection in swine herds, Manitoba, Canada. Emerg. Infect. Dis., 16, 706-708.

Perlroth, D. J., R. J. Glass, V. J. Davey, D. Cannon, A. M. Garber and D. K. Owens, 2010: Health outcomes and costs of community mitigation strategies for an influenza pandemic in the United States. Clin. Infect. Dis., 50, 165-174.

Pourbohloul, B., A. Ahued, B. Davoudi, R. Meza, L. A. Meyers, D. M. Skowronski, I. Villaseñor, F. Galván, P. Cravioto, D. J. D. Earn, J. Dushoff, D. Fisman, W. J. Edmunds, N. Hupert, S. V. Scarpino, J. Trujillo, M. Lutzow, J. Morales, A. Contreras, C. Chávez, D. M. Patrick and R. C. Brunham, 2009: Initial human transmission dynamics of the pandemic (H1N1) 2009 virus in North America. Influenza Other Respi. Viruses, 3, 215-222.

Rao, D. M., A. Chernyakhovsky and V. Rao, 2009: Modeling and analysis of global epidemiology of avian influenza. Environ. Model. Softw., 24, 124-134.

Riley, S., C. Fraser, C. A. Donnelly, A. C. Ghani, L. J. Abu-Raddad, A. J. Hedley, G. M. Leung, L. M. Ho, T. H. Lam, T. Q. Thach, P. Chau, K. P. Chan, S. V. Lo, P. Y. Leung, T. Tsang, W. Ho, K. H. Lee, E. M. Lau, N. M. Ferguson and R. M. Anderson, 2003: Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. Science, 300, 1961-1966.

Rios-Doria, D. and G. Chowell, 2009: Qualitative analysis of the level of cross-protection between epidemic waves of the 1918-1919 influenza pandemic. J. Theor. Biol., 261, 584-592.

Roberts, M. G., M. Baker, L. C. Jennings, G. Sertsou and N. Wilson, 2007: A model for the spread and control of pandemic influenza in an isolated geographical region. J. R. Soc. Interface, 4, 325-330.

Saenz, R. A., H. W. Hethcote and G. C. Gray, 2006: Confined animal feeding operations as amplifiers of influenza. Vector Borne Zoonotic Dis., 6, 338-346.

Savill, N. J., S. G. St Rose, M. J. Keeling and M. E. J. Woolhouse, 2006: Silent spread of H5N1 in vaccinated poultry: a chink in the protection of a caged flock can dramatically increase the chances of a flu outbreak. Nature, 442, 757-757.

Sertsou, G., N. Wilson, M. Baker, P. Nelson and M. G. Roberts, 2006: Key transmission parameters of an institutional outbreak during the 1918 influenza pandemic estimated by mathematical modelling. Theor. Biol. Med. Model., 3, 38.

Shaban, N., M. Andersson, A. Svensson and T. Britton, 2009: Household epidemics: modelling effects of early stage vaccination. Biom. J., 51, 408-419.

Sharkey, K. J., R. G. Bowers, K. L. Morgan, S. E. Robinson and R. M. Christley, 2008: Epidemiological consequences of an incursion of highly pathogenic H5N1 avian influenza into the British poultry flock. Proc. Biol. Sci., 275, 19-28.

Tiensin, T., M. Nielen, H. Vernooij, T. Songserm, W. Kalpravidh, S. Chotiprasatintara, A. Chaisingh, S. Wongkasemjit, K. Chanachai, W. Thanapongtham, T. Srisuvan and A. Stegeman, 2007: Transmission of the highly pathogenic avian influenza virus H5N1 within flocks during the 2004 epidemic in Thailand. J. Infect. Dis., 196, 1679-1684.

Tsai, M. T., T. C. Chern, J. H. Chuang, C. W. Hsueh, H. S. Kuo, C. J. Liau, S. Riley, B. J. Shen, D. W. Wang, C. H. Shen and T. S. Hsu Corresponding Author, 2010: Efficient simulation of the spatial transmission dynamics of influenza. PLoS Curr. Influenza., RRN1141.

Tuite, A., D. N. Fisman, J. C. Kwong and A. Greer, 2009: Seasonal Influenza Vaccine Allocation in the Canadian Population during a Pandemic. PLoS Curr. Influenza., RRN1143.

Tuite, A. R., A. L. Greer, M. Whelan, A. L. Winter, B. Lee, P. Yan, J. Wu, S. Moghadas, D. Buckeridge, B. Pourbohloul and D. N. Fisman, 2010: Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza. Can. Med. Assoc. J., 182, 131-136.

van den Dool, C., M. J. Bonten, E. Hak, J. C. Heijne and J. Wallinga, 2008: The effects of influenza vaccination of health care workers in nursing homes: insights from a mathematical model. PLoS Med., 5, e200.

van der Goot, J. A., M. C. de Jong, G. Koch and M. Van Boven, 2003: Comparison of the transmission characteristics of low and high pathogenicity avian influenza A virus (H5N2). Epidemiol. Infect., 131, 1003-1013.

van der Goot, J. A., G. Koch, M. C. de Jong and M. van Boven, 2005: Quantification of the effect of vaccination on transmission of avian influenza (H7N7) in chickens. Proc. Natl. Acad. Sci. U. S. A., 102, 18141-18146.

van der Goot, J. A., M. van Boven, G. Koch and M. C. de Jong, 2007: Variable effect of vaccination against highly pathogenic avian influenza (H7N7) virus on disease and transmission in pheasants and teals. Vaccine, 25, 8318-8325.

Vardavas, R., R. Breban and S. Blower, 2007: Can influenza epidemics be prevented by voluntary vaccination? PLoS Comput. Biol., 3, e85.

Viboud, C., P. Y. Boelle, S. Cauchemez, A. Lavenu, A. J. Valleron, A. Flahault and F. Carrat, 2004: Risk factors of influenza transmission in households. Br. J. Gen. Pract., 54, 684-689.

Vincent, A. L., K. M. Lager, K. S. Faaberg, M. Harland, E. L. Zanella, J. R. Ciacci-Zanella, M. E. Kehrli, Jr., B. H. Janke and A. Klimov, 2010: Experimental inoculation of pigs with pandemic H1N1 2009 virus and HI cross-reactivity with contemporary swine influenza virus antisera. Influenza Other Respi. Viruses, 4, 53-60.

Vincent, A. L., K. M. Lager, M. Harland, A. Lorusso, E. Zanella, J. R. Ciacci-Zanella, M. E. Kehrli and A. Klimov, 2009: Absence of 2009 pandemic H1N1 influenza A virus in fresh pork. PLoS One, 4, e8367. doi: 8310.1371/journal.pone.0008367.

Vu, T., S. Farish, M. Jenkins and H. Kelly, 2002: A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community. Vaccine, 20, 1831-1836.

Vynnycky, E. and R. White, 2010: An introduction to infectious disease modelling. Oxford University Press, Oxford, UK.

Weycker, D., J. Edelsberg, M. Elizabeth Halloran, J. I. M. Longini, A. Nizam, V. Ciuryla and G. Oster, 2005: Population-wide benefits of routine vaccination of children against influenza. Vaccine, 23, 1284-1293.

Wood, J. G., N. Zamani, C. R. MacIntyre and N. G. Becker, 2007: Effects of internal border control on spread of pandemic influenza. Emerg. Infect. Dis., 13, 1038-1045.

Woolhouse, M. E. and S. Gowtage-Sequeria, 2005: Host range and emerging and reemerging pathogens. Emerg. Infect. Dis., 11, 1842-1847.

Wu, J. T., S. Riley, C. Fraser and G. M. Leung, 2006: Reducing the impact of the next influenza pandemic using household-based public health interventions. PLoS Med., 3, e361-e361.

Yang, Y., J. D. Sugimoto, M. E. Halloran, N. E. Basta, D. L. Chao, L. Matrajt, G. Potter, E. Kenah and I. M. Longini, Jr., 2009: The transmissibility and control of Pandemic Influenza A (H1N1) virus. Science, 326, 729-733.

Yasuda, H. and K. Suzuki, 2009: Measures against transmission of pandemic H1N1 influenza in Japan in 2009: simulation model. Euro Surveill, 14, 19385-19385.

Zimmer, S. M. and D. S. Burke, 2009: Historical perspective-Emergence of influenza A (H1N1) viruses. N. Engl. J. Med., 361, 279-285.

Table 2.1: Inventory of modeling software/platforms either specifically developed and/or used for influenza spread in human and animal Populations.

Platform	Description	Agent	Question of interest	Spread type	Article
AnyLogic	General modeling platforms that supports all three major modeling approaches; system dynamics, discrete event simulation, agent-based modeling and hybrid of any of these models	Pandemic influenza A/H1N1 2009[1] Novel influenza virus[2]	I (all articles)	Human-human (all articles)	(Tuite et al., 2009, Tuite et al., 2010)[1] (Epstein et al., 2007)[2]
Berkeley Madonna	General modeling platform	Pandemic influenza A/H1N1 2009	P	Human-human	(Fraser et al., 2009)
EpiFlex	Stochastic individual-based modeling platform	Influenza viruses	T	Human-human	(Hanley, 2006)
FluTE	Stochastic individual-based network model	Pandemic influenza A/H2N2 1957-1958 and A/H1N1 2009	MT	Human-human	(Chao et al., 2010)
GLEaM (Global Epidemic and Mobility Modeler) - Metapopulation stochastic model on global scale	Stochastic metapopulation modeling platform for modeling large-scale spread of influenza viruses	Pandemic influenza viruses	MS	Human-human	(Balcan et al., 2009)
InfluSim	Deterministic homogeneous mixing compartmental model	Influenza virus in general	T	Human-human	(Duerr et al., 2007, Eichner et al., 2007)
MATLAB	General modeling platform	Pandemic influenza A/H1N1 1918-1919	P	Human-human	(Chowell et al., 2007b)
PIPM (Pandemic Influenza Policy Model)	Stochastic agent-based/individual-based model	Pandemic influenza viruses	T	Human-human	(Feighner et al., 2009)
RePAST (Recursive Porous Agent Simulation Toolkit)	Stochastic agent-based general modeling platform	Pandemic influenza A/H1N1 1918-1919	MS	Human-human	(Carpenter and Sattenspiel, 2009)
SEARUMS (Studying the Epidemiology of Avian Influenza Rapidly Using Modeling and Simulation)	Stochastic agent-based spatially explicit model	Avian influenza A/H5N1	MT	Bird-bird and bird-human	(Rao et al., 2009)

Key: I = evaluate different intervention strategies; M = describe new modeling methods and approaches; P = parameter estimation; S, evaluate spread; T = development of modeling software/platforms. Combination of these letters indicates combination of research questions of interest. Superscript numbers on agents corresponds to that of articles.

Table 2.2: Natural history parameters of influenza infection in humans estimated with 95% confidence intervals (CI) either from experimental, observational or modeling studies.

Disease states	Agent	Mean (95% CI) in days	References
1. Incubation period	1. Pandemic influenza A/H1N1 2009	4.3 (2.6–6.6)	(Tuite et al., 2010)
2. Latent period	1. Pandemic influenza A/H1N1 2009	2.6 (2.4–3.1)	(Tuite et al., 2010)
3. Subclinical infectious period	1(a). Pandemic influenza A/H1N1 1918 (Spring wave)	2.9 (2.8–3.1)	(Chowell et al., 2006a)
	1(b). Pandemic influenza A/H1N1 1918 (Autumn wave)	2.2 (1.9–2.7)	(Chowell et al., 2006a)
4. Clinical infectious period	1(a). Pandemic influenza A/H1N1 1918 (Spring wave)	1.2 (1.1–1.3)	(Chowell et al., 2006a)
	1(b). Pandemic influenza A/H1N1 1918 (Autumn wave)	2.6 (2.43–2.8)	(Chowell et al., 2006a)
	2. Pandemic influenza A/H1N1 2009	3.4 (2.1–4.7)	(Tuite et al., 2010)
	3. Seasonal influenza A/H1N1	4.5 (3.7–5.3)	(Carrat et al., 2008)
	4. Seasonal influenza A/H3N2	5.1 (4.5–5.8)	(Carrat et al., 2008)
	5. Influenza viruses	4.8 (4.3–5.3)	(Carrat et al., 2008)

Table 2.3: Natural history parameters of influenza infection in humans estimated without 95% confidence interval, referenced or assumed for modeling. All values are reported in days. Summary estimates are medians (ranges) of means, minimum and maximum values of two or more articles. Single value represented value from either a single article or exactly same value from two or more articles.

Disease states	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
1. Incubation period				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	2.0	1.0 (1.0–2.0)	-
	2. Seasonal influenza A/H1N1	-	1.0	-
	3. Seasonal influenza virus A/H3N2	2.0	1.0	3.0
b) Referenced values	1. Pandemic influenza A/H1N1 1918	1.0	-	-
	2. Pandemic influenza A/H1N1 2009	2.0 (1.5–3.0)	1.0	5.0
	3. Novel influenza viruses	1.9 (1.0–2.0)	1.0	3.0
	4. Seasonal influenza virus A/ H1N1	-	1.0	4.0
	5. Seasonal influenza virus A/H3N2	-	1.0	3.5 (3.0–4.0)
	6. Influenza viruses	2.4 (1.9–2.9)	1.0	3.0 (3.0–4.0)
c) Assumed values	1. Pandemic influenza A/H1N1 2009	-	1.0	3.0
	2. Novel influenza viruses	2.0	-	-
2. Latent period				
a) Estimated values	1. Influenza viruses	1.0	-	-
b) Referenced values	1. Pandemic influenza A/H1N1 1918	1.9 (1.0–3.5)	1.2 (0.8–1.5)	1.7 (1.5–1.9)
	2. Pandemic influenza A/H2N2 1957	1.9	-	-
	3. Pandemic influenza A/H1N1 2009	1.5 (1.0–3.5)	0.9 (0.7–1.0)	4.0 (2.0–5.0)
	4. Novel influenza viruses	1.5 (0.5–2.0)	1.0 (1.0–1.2)	2.0

Table 2.3: (continued)

Disease states	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
	5. Seasonal influenza A/H1N1	1.9	1.0	3.0
	6. Seasonal influenza A/H3N2	1.9	1.0	3.0
	7. Influenza viruses	1.9 (0.6–2.1)	1.0	3.0 (2.0–3.0)
c) Assumed values	1. Pandemic influenza A/H1N1 2009	2.0	1.0	3.0
	2. Novel influenza viruses	2.3 (1.5–3.0)	-	-
	3. Influenza viruses	1.0	-	-
3. Subclinical infectious period				
a) Estimated values	1. Pandemic influenza A/H1N1 1918	-	-	-
b) Referenced values	1. Pandemic influenza A/H1N1 2009	1.0 (0.5–2.5)	-	2.0
	2. Novel influenza viruses	1.0 (0.3–4.1)	0.5	0.7
	3. Influenza viruses	3.0 (0.5–4.1)	-	-
c) Assumed values	1. Novel influenza viruses	0.5	-	-
4. Clinical infectious period				
a) Estimated values	1. Pandemic influenza A/H1N1 1918	1.8 (1.7–3.0)	1.7 (1.6–1.7)	1.9 (1.8–1.9)
	2. Pandemic influenza A/H1N1 2009	5.6	1.0	10.0 (8.0–12.0)
	3. Seasonal influenza A/H3N2	3.8	3.1	4.6
b) Referenced values	1. Pandemic influenza A/ H1N1 1918	4.6 (4.1–5.0)	2.6 (1.5–3.3)	4.15 (2.9–10)
	2. Pandemic influenza A/H2N2 1957	4.1	-	-
	3. Pandemic influenza A/H1N1 2009	3.8 (2.5–7.0)	3.8 (1.9–4.0)	5.5 (2.9–10)
	4. Novel influenza viruses	4.0 (1.0–7.0)	3.3 (2.5–5.0)	7.0 (4.1–12.0)
	5. Seasonal influenza A/H1N1	4.1	2.0	8.0
	6. Seasonal influenza A/H3N2	4.1(3.8–4.1)	2.0	8.0
	7. Influenza viruses	4.1 (1.4–7.0)	3.0 (2.0–3.0)	6.0 (6.0–10.0)
c) Assumed values	1. Pandemic influenza A/H2N2 1957	-	3.8	5.3
	2. Pandemic influenza A/H3N2 1968	3.0	-	-
	3. Pandemic influenza A/H1N1 2009	5.0 (3.0–5.0)	3.0	7.0
	4. Novel influenza viruses	4.0	2.0	3.0
	5. Influenza viruses	3.0	-	-
5. Immunity period	1. Novel influenza viruses	-	365	-
6. Pre-existing immunity (%)				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	4.0	34.0
b) Referenced values	1. Pandemic influenza A/H1N1 1918	50.0	10.0	20.0
	2. Pandemic influenza A/H1N1 2009	34.0 (5.0–50.0)	30.0	50.0 (15.0–70.0)
	3. Novel influenza viruses	30.0	-	63.5 (27.0–100.0)
	4. Seasonal influenza A/H3N2	-	-	27.0
	5. Influenza viruses	-	-	30.0
c) Assumed values	1. Novel influenza viruses	25.0	-	-
	2. Influenza viruses	-	-	62.5 (50.0–75.0)

(a) Estimated values = those estimated from empirical data of experimental or observational studies; (b) Referenced values = those values taken from other articles; (c) Assumed values = values assumed based on expert's opinion and other unpublished sources. These definitions apply to subsequent tables from Table 2.4 to Table 2.15.

Table 2.4: Natural history parameters of influenza infection in birds estimated with 95% CI either from experimental, observational or modeling studies.

Disease states	Agent	Mean (95% CI) in days	References
Clinical infectious period	1. Highly pathogenic avian influenza A/H5N2	6.8 (4.9–8.7)	(van der Goot et al., 2003)
	2. Low pathogenic avian influenza A/H5N2	4.3 (2.6–5.9)	(van der Goot et al., 2003)
	3. Highly pathogenic avian influenza A/H7N7	6.3 (3.9–8.7)	(van der Goot et al., 2005)

Table 2.5: Natural history parameters of influenza infection in swine and birds estimated (without 95% CI), referenced or assumed for modeling.

Species and disease states	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Swine				
1. Incubation period				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	1.0 (1.0–2.0)	2.5 (1.0–3.0)
2. Latent period				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	1.0	2.0 (2.0–5.0)
	2. Swine influenza H1N1 virus	-	-	3.0
3. Clinical infectious period				
a) Estimated values	1(a). Pandemic influenza A/H1N1 2009 (Individual level)	-	7.0 (3–7.0)	8.0 (5.0–15.0)
	1(b). Pandemic influenza A/H1N1 2009 (Herd level)	-	10.0	31 (20.0–42.0)
	2. Swine influenza A/H1N1	-	3.0	5.0
b) Referenced values	1. Novel influenza virus	7.0	-	-
4. Immunity period				
a) Estimated values	1. Swine influenza A /H1N1	-	365.0	692.5 (545.0–840.0)
B. Birds				
1. Incubation period				
a) Referenced values	1(a). Avian influenza A/H5N1 (Individual level)	5.0	-	-
	1(b). Avian influenza A/H7N1 (Individual level)	-	-	6.0
	2. Avian influenza A/H7N7	-	-	3.0
b) Assumed values	1. Avian influenza A/H7N1	-	2.0	-
	2. Avian influenza A/H7N7	-	1.0	-
2. Latent period				
b) Referenced values	1. Avian influenza A/H5N1	1.75 (1.5–2.0)	1.0	2.0
	2. Avian influenza A/H7N7	2.0	-	-
c) Assumed values	1. Avian influenza A/H7N7	2.0	-	-
3. Subclinical infectious period				
b) Referenced values	1. Avian influenza A/H5N1	1.0	-	-
	2. Avian influenza A/H7N7	4.0	-	6.0
4. Clinical infectious period				
b) Referenced values	1(b). Avian influenza A/H5N1 (Flock level)	10.0	-	-
	2(a). Avian influenza A/H7N7 (Individual level)	6.3	1.0	6.0
	2(b). Avian influenza A/H7N7 (Flock level)	13.8	4.0	12.0
	3. Avian influenza virus	14.0	-	-
c) Assumed values	1. Avian influenza A/H5N1 (Village level)	7.0	-	-

Table 2.6: Distributions of natural history parameters of influenza infection in human and bird populations estimated from experimental, observational studies, referenced from other articles, or assumed for modeling.

Species and disease states	Agent	Distribution
A. Human		
1. Incubation period		
a) Estimated values	1. Pandemic influenza A/H1N1 2009	Log-normal with a mean of 4.3 days and 95%CI 2.6–6.6 days.
b) Referenced/assumed values	1. Pandemic influenza A/H1N1 2009	Uniform with a range of 1–3 days; Exponential with a mean of 1.4 days.
	2. Novel influenza viruses	Mean of 1.9 days with empirical distribution of 1 day (30%); 2 days (50%); 3 days (20%); Gamma with a mean of 1.9 days and coefficient of variation of 37.8%.
	3. Seasonal influenza viruses	Right-shifted Weibull with a fixed offset of 0.5 day (lower bound cut-off value), shape parameter of 2.21 (95% CI 1.36–3.37) and scale parameter of 1.10 (95%CI 0.83–1.42) resulting in a mean incubation period of 1.48 days and standard deviation of 0.47 day.
2. Latent period		
a) Estimated values	1. Novel influenza viruses	Right-shifted Weibull with a fixed offset of 0.5 day (lower bound cut-off value), shape parameter of 2.24 and scale parameter of 1.11.
b) Referenced/assumed values	1. Pandemic influenza A/H1N1 2009	Exponential with a mean of 1.25 days with an offset of 0.75 day (lower bound cut-off value).
	2. Novel influenza viruses	Mean of 1.9 days with empirical distribution of 1 day (30%) 2 days (50%) and 3 days (20%); Exponential with a mean of 1.2 days; Exponential with a mean of 1.4 days; Right-shifted Weibull with a fixed offset of 0.5 day (lower bound cut-off value), shape parameter of 2.24 and scale parameter of 1.11; Weibull with a fixed offset of 0.5 day (lower bound cut-off value), shape parameter of 2.21 and variable scale parameter values selected based on the serial intervals (which in turn were randomly selected from a range between latent and infectious periods).
	3. Seasonal influenza viruses	Exponential around mean of 1.25 days with an offset of 0.75 day (lower bound cut-off value).
3. Clinical infectious period		
b) Referenced/assumed values	1. Pandemic influenza A/ H1N1 1918	Exponential around a mean of 3 days.
	2. Pandemic influenza A/H1N1 2009	Exponential around mean of 3 days; gamma with mean varied between 3.8–5.5 days ; uniform with a range of 3–7 days; log-normal with a mean of 9.3 (95% CI 2.6–24.2) days.
	3. Novel influenza viruses	Mean of 4.1 days with empirical distribution of 3 days (30%); 4 days (4%); 5 days (20%); 6 days (10%); exponential around a mean of 3 days; log-normal with a mean of log(-0.72 and 95%CI -1.64– -0.09 days) and a standard deviation of log(1.8 and 95%CI 1.3–2.5 days); gamma with a mean of 5 days and coefficient of variation of 33.3%.
	4. Seasonal influenza A/H1N1	Log-normal with variable median values selected based on serial intervals (which in turn were randomly selected from a range between latent and infectious periods) and a variance of 0.23.
	5. Seasonal influenza A/H3N2	Gamma with a mean of 3.8 days and standard deviation of 2 days, and infectious period truncated at 10 days; gamma with scale parameter of 2 days and shape parameter of 2.05 days.
	6. Influenza viruses	Exponential with mean of 3 days; Exponential with a mean of 1.4 days; Mean of 4.1 days and empirical distribution of 3 days (30%), 4 days (40%), 5 days (20%), 6 days (10%).

Table 2.6: (Continued)

Species and disease states	Agent	Distribution
B. Bird		
1. Latent period		
b) Referenced/assumed values	1. Avian influenza A/H5N1	Latent period of 48 hours + Binomial(48, 0.25) where p = probability of remaining in the latent period; Normal with a mean of 1.5 days and standard deviation of 1 day.
	2. Avian influenza A/H7N7	Gamma with a mean of 0.159 per day with a shape parameter of 20.
2. Subclinical infectious period		
b) Referenced/assumed values	1. Avian influenza A/H5N1	Subclinical infectious period of 24 hours + Binomial(24, 0.25) where p = probability of remaining in this state.
3. Clinical infectious period		
b) Referenced/assumed values	1. Avian influenza A/H5N1	Binomial(96, 0.05) where p = probability of remaining in this state (unit in hours)
	2. Avian influenza A/H5N1	Gamma with a mean of 0.159 per day with a shape parameter of 20; exponential around a mean of 6.3 days with 95%CI 3.9–8.7 days.

Table 2.7: Summary of daily contact frequencies in human and bird populations estimated either from survey, referenced from other articles or assumed for modeling.

Species	Contacts category	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Human-human	A. Age			
a) Estimated values	<5	10.21 (7.65)	-	-
	5-9	14.81 (10.09)	-	-
	10–14	18.69 (13.4)	-	-
	15–19	19.93 (21.14)	-	-
	20–29	17.18 (25.72)	-	-
	30–39	17.83 (21.68)	-	-
	40–49	17.51 (23.29)	-	-
	50–59	15.96 (20.84)	-	-
	60–69	10.51 (14.47)	-	-
	70+	7.71 (10.97)	-	-
	B. Household			
	Household size 1	11.23 (18.26)	-	-
	Household size 2	13.32 (17.89)	-	-
	Household size 3	14.67 (16.44)	-	-
	Household size 4	17.71 (17.67)	-	-
	Household size 5	19.49 (29.12)	-	-
	Household size 6+	19.3 (13.14)	-	-
	C. Students			
	Students -classmates	38.4	-	-
	Students –non-classmates	14.8	-	-
b) Referenced values	A. Activity based			
	1. Low activity	2.0	-	-
	2. Medium activity	10.0	-	-
	3. High activity	50.0	-	-
	B. Age group			
	1. Children (0–11 years)	14.0 (3.0–24.0)	-	-
	2. Teen (12–18 years)	4.0 (3.0–4.0)	-	-
	3. Adult (19–64 years)	6.0 (3.0–13.0)	-	-
	4. Senior (65+ years)	4.0 (3.0– 5.0)	-	-

Table 2.7: (Continued)

Species	Contacts category	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
	C. Occupational/community structure			
	1. Community in general	16.0 (1.0–32.0)	5.0 (5.0–14.0)	27.0 (24.0–50.0)
	2. Health care worker - coworkers	2.0 (2.0–8.0)	-	-
	3. Health care worker with patients	30.0	-	-
	4. Student with classmates	14.0 (14.0–15.0)	-	-
	5. Student with non-classmates	15.0	-	-
c) Assumed values	A. Age group			
	1. Children (0-11 years)	6.0	-	-
	B. Community structure			
	1. Community in general	1.0 (1.0–2.0)	-	1.0
B. Bird-bird				
a) Estimated values	1. Maximum farms visited by feed lorry/trip	-	-	6.0
b) Referenced values	1. Flock to flock contact rate/day	-	0.2	0.3
c) Assumed values	1. Inter-company contact /day	3.0	-	-
	2. Maximum farms visited by slaughter lorry/day	-	-	4.0

Table 2.8: Summary estimates of transmission probability per contact of influenza viruses in humans and birds estimated, referenced, or assumed for modeling.

Species and transmission parameter	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Human-human (all contact types combined)				
a) Estimated/calibrated values	1. Pandemic influenza A/H1N1 1918	0.51		-
	2. Novel influenza viruses	0.24 (0.1–0.024)	-	-
	3. Influenza viruses	0.24	0.39	0.78
b) Referenced values	1. Pandemic influenza A/H1N1 2009	0.0435 (0.00255–0.6)	-	-
	2. Novel influenza viruses		0.55 (0.5–0.6)	0.7
	3. Influenza viruses		0.2503 (0.0006–0.5)	0.0012
B. Bird-bird				
c) Assumed values	1. Avian influenza A/H5N1(within flock/day)	0.5	-	-
	2. Avian influenza A/H5N1 (per dangerous slaughterhouse contact)	0.25	-	-

Table 2.9: Summary of transmission coefficients/rates of influenza infection in humans, birds, and swine estimated, referenced or assumed for modeling.

Species and transmission parameter	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
I. Discrete time (8, 12 or 24 hourly intervals)				
A. Human-human				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	0.060192 (0.0095–0.060192)	0.00001	0.6
	2. Novel influenza viruses	0.00058	0.00029	0.00102
	3. Influenza viruses	-	0.000005	0.08
b) Referenced values	1. Pandemic influenza A/ H2N2 1957	0.0125 (0.00001–0.08)	-	-
c) Assumed values	1. Novel influenza viruses	-	0.58	0.64
B. Bird-Bird				
a) Estimated values	1. Avian influenza A/H5N1 (bird level)	2.66	2.01	2.55
	2. Avian influenza A/H5N1 (flock level)	0.66	0.5	0.87
	3. Avian influenza A/H5N2 (bird level)	0.24	0.12	0.45
	4. Avian influenza A/H7N7 (bird level)	33.0	-	
	5. Avian influenza viruses	0.22	-	0.42
C. Zoonotic spread	1. Novel influenza virus			
c) Assumed values	a) Bird-human	0.012	-	-
	b) Human-human	0.03	-	-
II. Continuous time (seconds to hourly)				
A. Human-human				
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	0.00001	0.0125
	2. Influenza viruses	0.581	0.199	0.425
b) Referenced values	1. Novel influenza virus	0.00017	-	-
B. Zoonotic spread				
1. Between bird-human	1. Novel influenza virus			
c) Assumed values	a) Bird-bird	0.15 (0.1–0.2)	-	-
	b) Human-human	0.0006	0.0015	0.0025 (0.002–0.003)
2. Animal-human	1. Novel influenza virus			
c) Assumed values	a) Swine-swine	0.2857	-	-
	b) Swine-human	0.00123	-	-
	c) Human-human	0.3	-	-
	d) Human-swine	0.122851	-	-

Table 2.10: Estimates of basic reproduction numbers (R_0) with 95% CI of influenza infection in human population estimated either from experimental, observational or modeling studies.

Agent	Mean (95% CI)	Reference
1(a). Pandemic influenza A/H1N1 1918 (using first 10 days data of spring wave of Geneva)	1.6 (1.5–1.7)	(Chowell et al., 2007a)
1(b). Pandemic influenza A/H1N1 1918 (using first 10 days data of autumn wave of Geneva)	3.1 (2.8–1.7)	(Chowell et al., 2007a)
1(c). Pandemic influenza A/H1N1 1918 (using non-hospitalized and asymptomatic cases of 1st phase/spring wave in Geneva)	1.5 (1.5–1.5)	(Chowell et al., 2006a)
1(d). Pandemic influenza A/H1N1 1918 (using non-hospitalized and asymptomatic cases of 2nd phase/autumn wave of Geneva)	3.8 (3.6–3.9)	(Chowell et al., 2006a)
1(e). Pandemic influenza A/H1N1 1918 (using early exponential growth phase of autumn wave daily case notification data of San Francisco, California)	3.0 (2.7–3.3)	(Chowell et al., 2007b)
1(f). Pandemic influenza A/H1N1 1918 (using deterministic SIR compartmental model of daily case notification data of autumn wave in San Francisco, California)	2.4 (2.2–2.6)	(Chowell et al., 2007b)
1(g). Pandemic influenza A/H1N1 1918 (using complex SEIR model of daily case notification data of autumn wave in San Francisco, California)	2.2 (1.6–2.1)	(Chowell et al., 2007b)
1(h). Pandemic influenza A/H1N1 1918 (using SIR Bayesian approach of daily case notification data of autumn wave in San Francisco, California)	2.1 (1.1–3.0)	(Chowell et al., 2007b)
1(i). Pandemic influenza A/H1N1 1918	2.0 (1.7–2.3)*	
2(a). Pandemic influenza A/H1N1 2009	1.3 (1.3–1.4)	(Tuite et al., 2010)
2(b). Pandemic influenza A/H1N1 2009	1.4 (1.4–1.5)	(Pourbohloul et al., 2009)
2(c). Pandemic influenza A/H1N1 2009 (using intrinsic growth rate and generation interval obtained from households study)	2.2 (2.1–2.4)	(Boëlle et al., 2009)
2(d). Pandemic influenza A/H1N1 2009 (using intrinsic growth rate and generation interval obtained from viral excretion of experimental influenza infection study)	2.6 (2.4–2.8)	(Boëlle et al., 2009)
2(e). Pandemic influenza A/H1N1 2009 (using intrinsic growth rate and generation interval obtained from hypothetical distribution from Elveback et al., (1976)	3.1 (2.9–3.5)	(Boëlle et al., 2009)
2(f). Pandemic influenza A/H1N1 2009 (using real time estimation of averaging the number of secondary cases across all possible chains of transmissions of epidemic curve)	3.2 (2.1–4.0)*	(Boëlle et al., 2009)
3. Seasonal influenza A/H1N1	1.2 (0.8–1.7)*	(Chen and Liao, 2010)
4. Seasonal influenza A/H3N2	1.4 (0.9–2.2)*	(Chen and Liao, 2010)
5. Influenza viruses	1.3 (1.2–1.4)	(Chowell et al., 2008b)

* Median and its 95% CI values instead of mean

Table 2.11: Summary of basic reproductive number (R_0) of influenza infection in human, bird and swine populations estimated, referenced or assumed for modeling.

Species and transmission parameter	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Human-human				
a) Estimated values	1. Pandemic influenza A/H1N1 1918	2.2 (1.8–2.7)	1.3 (1.2–2.8)	2.2 (1.2–3.1)
	2. Pandemic influenza A/H3N2 1968	-	1.2	3.0
	3. Pandemic influenza A/H1N1 2009	1.5	1.34 (1.1–2.3)	1.9 (1.3–2.9)
	4. Novel influenza viruses	2.1	1.5	1.8
	5. Seasonal influenza A/H1N1	1.1	-	1.4
	6. Seasonal influenza A/H3N2	1.5 (1.4–1.7)	1.4 (1.3–1.5)	1.7 (1.6–1.8)
	7. Influenza viruses (between households)	3.9 (2.0–6.0)	-	-
b) Referenced values	1. Pandemic influenza A/H2N2 1957	1.7 (1.7–1.7)	-	-
	2. Pandemic influenza A/H1N1 2009	1.5 (1.3–1.8)	1.3 (1.2–1.6)	2.0 (1.3–2.2)
	3. Novel influenza viruses	1.9 (1.4–3.1)	1.4 (0.3–1.9)	2.4 (1.4–3.3)
	4(a). Influenza viruses (individual level)	2.1 (1.7–2.5)	1.4 (1.3–1.6)	2.4 (1.4–2.73)
	4(b). Influenza viruses (between households)	1.2	-	-
c) Assumed values	1. Pandemic influenza A/H3N2 1968	-	1.5	3.5
	2. Pandemic influenza A/H1N1 2009	1.7	1.4	2.4
	3. Novel influenza viruses	1.9	1.3	2.3 (1.7–3.5)
	4. Influenza viruses	2.0	1.5	3.0
B. Bird-bird				
a) Estimated values	1(a). Avian influenza A/H5N1 (within flock)	-	25.0	66.0
	1(b). Avian influenza A/H5N1 (between villages)	2.5 (2.2–2.7)	2.0	2.1
	2(b). Avian influenza A/H7N1 (between farms)	-	0.6	1.8
	3(a). Avian influenza A/H7N7 (within flock)	-	1.3	-
	3(b). Avian influenza A/H7N7 (between farms)	3.3 (1.3–5.2)	3.6 (3.1–4.0)	6.7 (6.5–6.9)
b) Referenced values	1. Avian influenza A/H5N1 (within flock)	-	25.0	66.0
	2. Avian influenza A/H7N7 (between farms)	-	0.8	6.5
C. Zoonotic spread articles				
c) Assumed values	1. Novel influenza virus			
	a) Human-human	1.0	2.0 (0.6–3.5)	4.1 (1.1–7.1)
	b) Swine-swine	2.0	-	-
	c) Bird-bird	1.1	0.4 (0.1–0.8)	1.8 (1.1–2.5)

Table 2.12: Estimates of basic reproduction numbers (R_0) with 95% CI estimated either from experimental, observational or modeling studies in birds.

Agent	Mean (95% CI)	Reference
1(a). Highly pathogenic avian influenza A/H5N1 (within-flock using 1 day infectious period)	2.3 (2.0–2.6)	(Tiensin et al., 2007)
1(b). Highly pathogenic avian influenza A/H5N1 (within-flock using 4 days infectious period)	2.6 (2.0–3.5)	(Tiensin et al., 2007)
2. Highly pathogenic avian influenza A/ H5N2 (between flock level)	1.0 (0.0–2.4)	(van der Goot et al., 2003)
3. Low pathogenic avian influenza A/LPAI H5N2 (between flock level)	1.0 (0.0–2.3)	(van der Goot et al., 2003)

Table 2.13: Summary of basic reproductive number (R0) of influenza infection in bird and swine populations including zoonotic transmissions estimated, referenced or assumed for modeling.

Transmission parameter	Spread in species and agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Bird-bird				
a) Estimated values	1(a). Avian influenza A/H5N1 (within flock)	-	25.0	66.0
	1(b). Avian influenza A/H5N1 (between villages)	2.5 (2.2–2.7)	2.0	2.1
	2(b). Avian influenza A/H7N1 (between farms)	-	0.6	1.8
	3(a). Avian influenza A/H7N7 (within flock)	-	1.3	-
	3(b). Avian influenza A/H7N7 (between farms)	3.3 (1.3–5.2)	3.6 (3.1–4.0)	6.7 (6.5–6.9)
b) Referenced values	1. Avian influenza A/H5N1 (within flock)	-	25.0	66.0
	2. Avian influenza A/H7N7 (between farms)	-	0.8	6.5
C. Zoonotic spread				
c) Assumed values	1. Novel influenza virus			
	a) Human-human	1.0	2.0 (0.6–3.5)	4.1 (1.1–7.1)
	b) Swine-swine	2.0	-	-
	c) Bird-bird	1.1	0.4 (0.1–0.8)	1.8 (1.1–2.5)

Table 2.14: Summary estimates of generation intervals of influenza infection in human estimated, referenced or assumed for modeling.

Transmission parameter	Type of spread and agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
a) Estimated values	1. Pandemic influenza A/H1N1 1918	2.6	-	-
	2. Pandemic influenza A/H1N1 2009	3.5	2.6 (2.2–4.0)	3.2 (2.6–5)
	3. Seasonal influenza A/H1N1	2.1 (1.9–2.3)	1.6 (1.5–1.6)	3.8
	4. Seasonal influenza A/H3N2	3.1	2.2	4.0
	5. Influenza viruses	3.5 (3.4–3.6)	2.9	4.3
	6. Novel influenza viruses	2.4	1.0	3.9
b) Referenced values	1. Pandemic influenza A/ H1N1 1918	6.0	2.8 (2.6–3.0)	5.0 (4.0–6.0)
	2. Pandemic influenza A/H1N1 2009	3.0 (1.9–4.6)	1.6 (1–6.6)	5.0 (2.7–7.4)
	3. Novel influenza viruses	2.9 (2.6–3.4)	2.6 (2.1–3.0)	3.0 (2.7–3.8)
	4. Seasonal influenza A/H3N2	2.4	-	-
	5. Influenza viruses	2.8 (2.8–2.9)	-	-
c) Assumed values	1. Pandemic influenza A/H3N2 1968	3.9 (3.5–4.2)	-	-
	2. Novel influenza viruses	2.6	2.8	4.0

Table 2.15: Summary of intervention parameters estimated, referenced or assumed for modeling influenza infection in human and bird populations.

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)
A. Human				
1. Antiviral treatment (AV)				
a) Estimated values	1. AV efficacy	-	70.0	75.5 (61.0–90.0)
b) Referenced values	1. AV efficacy (%)	-	30.0 (28.0–30.0)	70.0 (30.0–100)
	2. Reduction in infectiousness (%)	-	30.0	60.0 (28.0–80.0)
	3. Reduction in susceptibility (%)	-	30.0 (25.0–30.0)	30.0 (30.0–90.0)
	4. AV coverage (%)	-	50.0 (0.0–60.0)	90.0 (50.0–100)
	5. AV treatment duration (day)	-	10.0 (5.0–10.0)	10.0 (5.0–10.0)
	6. AV use compliance (%)	-	48.0 (5.0–90.0)	90.0
c) Assumed values	1. AV efficacy (%)	-	50.0	30.0 (30.0–100)
	2. Reduction in infectiousness (%)	-	-	62.0 (30.0–100)
	3. Reduction in susceptibility (%)	-	-	30 (30.0–100)
	4. AV coverage (%)	-	50.0 (2.0–80.0)	100 (6.0–100)
	5. AV treatment duration (day)	-	7.5 (5.0–10.0)	5.0
	6. AV use compliance (%)	-	5.0	100 (80.0–100)
2. Vaccination				
a) Estimated values	1. Vaccine efficacy (%)	-	38.75 (19.0–58.5)	57.5 (47.0–68.0)
b) Referenced values	1. Vaccine efficacy (%)	-	40.0 (20.0–70.0)	73.0 (30.0–100)
	2. Reduction in infectiousness (%)	-	30.0 (20.0–50.0)	70.0 (40.0–90.0)
	3. Vaccine immune delay (days)	-	7.0	42.0
	4. Vaccination coverage (%)	60.0 (50.0–60.0)	25.5 (18.0–26.0)	87.5 (69.0–100.0)
c) Assumed values	1. Vaccine efficacy (%)	-	30.0 (5.0–50.0)	70.0 (30.0–100)
	2. Reduction in infectiousness (%)	-	50.0 (30.0–50.0)	80.0 (40.0–100)
	3. Vaccine immune delay (days)	-	15.0 (0.0–15.0)	14.0 (0.0–14.0)
	4. Vaccination coverage (%)	50.0 (30.0–50.0)	20.0 (0.0–50.0)	75.0 (7.0–100)
3. School closure				
c) Assumed values	1. School closure contact reduction (%)	75.0 (50.0–80.0)	31.5 (30.0–33.0)	25.0 (7.0–300.0)
	2. School closure duration (days)	14.0 (7.0 – 28.0)	7.0 (7.0–60.0)	7.0 (0.0–56.0)
	3. School closure delay (days)	-	0.0–14.0	
4. Quarantine				
c) Assumed values	1. Quarantine contact reduction (%)	50.0	55.0 (40.0–60.0)	85.0 (30.0–100)
	2. Quarantine period (days)	10.0 (2.0–10.0)	1.0	7.0 (3.0–21.0)
B. Birds				
1. Quarantine				
c) Assumed values	1. Quarantine period (days)	21.0–31.0	-	-

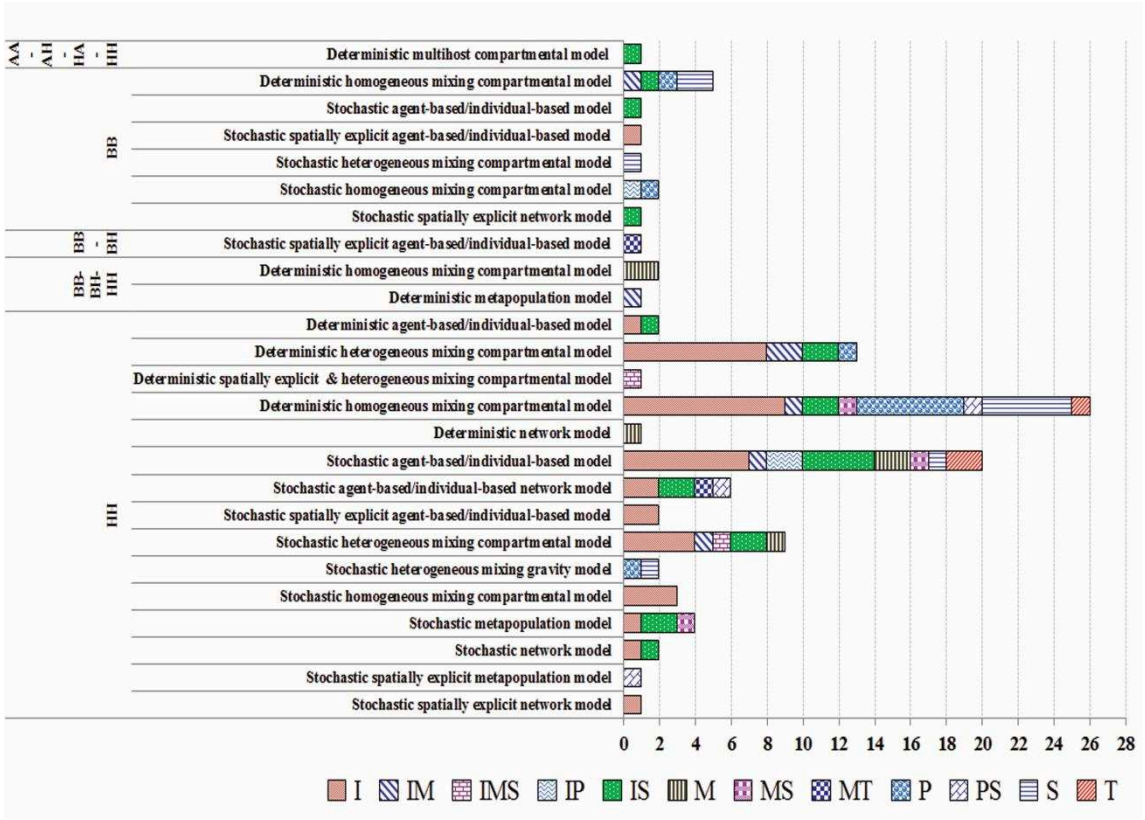

Figure 2.1: Different model types used for modeling spread of influenza viruses in human and animal populations to address various research questions. Key: I = evaluate intervention strategies; M = describe new modeling methods and approaches; P = estimate parameters; S = evaluate spread; T = develop modeling platform or tool. A combination of these letters indicates combination of research questions of interest. (a) AA-AH-HA-HH = spread within and between swine and human simultaneously; (b) BB = spread between bird species; (c) BB-BH = spread within bird species and birds to humans; (d) BB-BH-HH = spread between birds, birds to humans and humans to humans; (e) HH = spread between humans. No distinction of spread is made between individual, household, herd/flock or village levels.

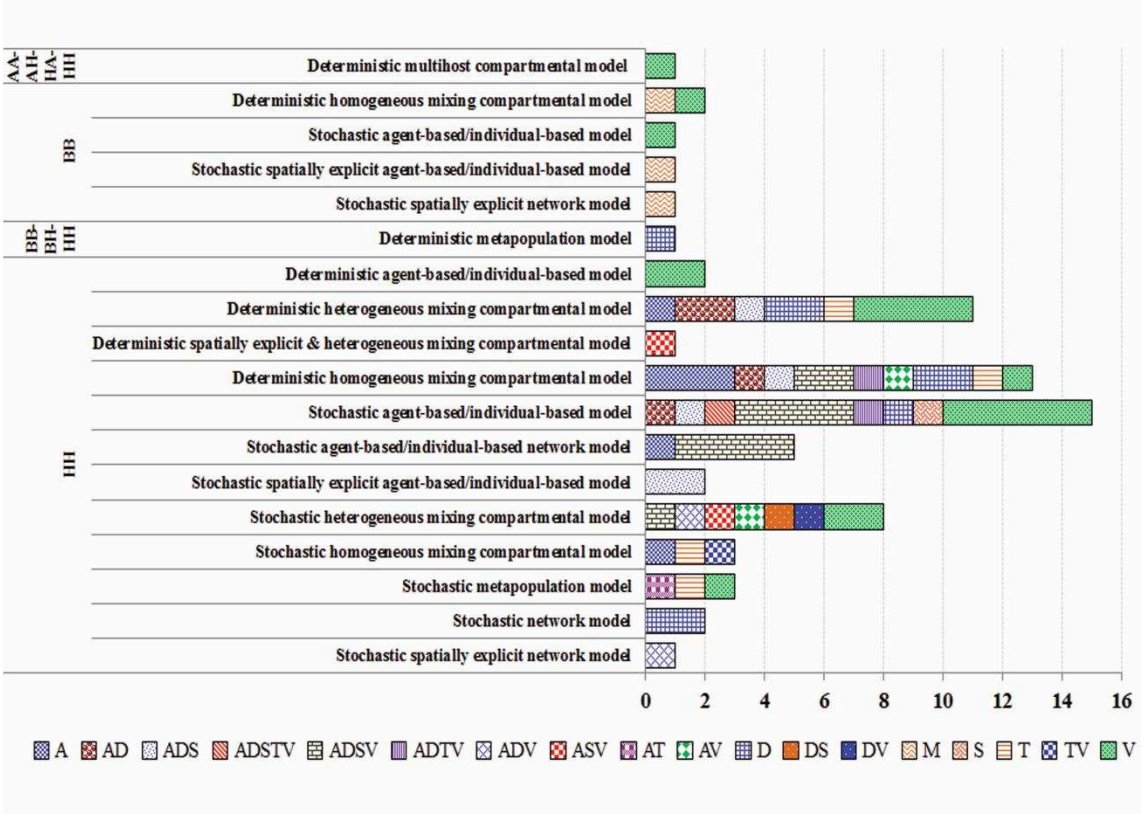

Figure 2.2: Different model types used for assessing various intervention strategies against influenza in human and animal populations. Key: A = antiviral for either or both prophylactic and treatment; D = include workplace closure, contact tracing, quarantine, isolation, cancellation of community and mass gathering, use of personal hygiene and protective equipment; M = movement control and depopulation in animals (including birds); S = specifically school and daycare closure; T = air travel restriction; V = vaccination prior to outbreak or during the outbreak. Combinations of letters indicate combination of these measures. (a) AA-AH-HA-HH = spread within and between swine and human simultaneously; (b) BB = spread between bird species; (c) BB-BH = spread within bird species and birds to humans; (d) BB-BH-HH = spread between birds, birds to humans and humans to humans; (e) HH = spread between humans. No distinction of spread is made between individual, household, herd/flock or village levels.

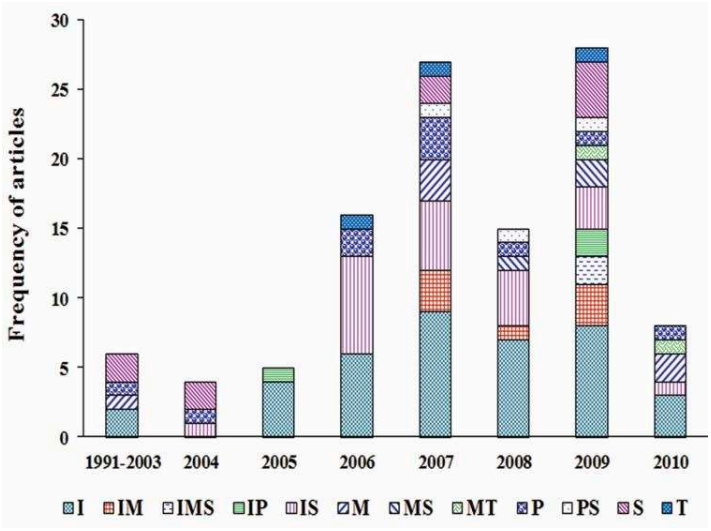

Figure 2.3: Temporal trend in the research questions of interest for modeling influenza viruses in human and animal populations. Temporal trend in the research questions of interest for modeling influenza viruses in human and animal populations. Key: I = evaluate intervention strategies; M = describe new modeling methods and approaches; P = estimate parameters; S = evaluate spread; T = develop modeling platform or tool. A combination of these letters indicates combination of research questions of interest.

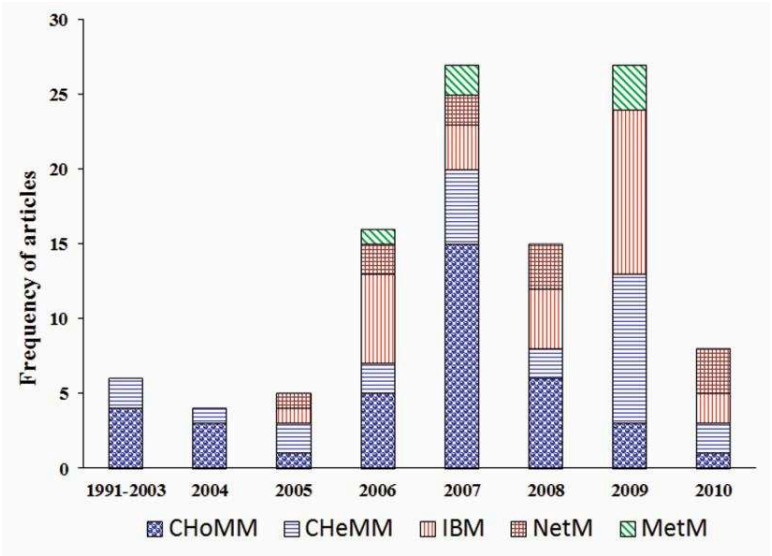

Figure 2.4: Temporal trend over the past decade in the types of modeling methods applied to research on influenza viruses spread and control in human and animal populations. Key: CHoMM = Compartmental homogeneous mixing models; CHeMM = Compartmental heterogeneous mixing models; IBM = Individual-based/agent-based model; NetM = Network models; MetM = Metapopulation models.

Chapter 3

One-Health Simulation Modeling: A Case Study of Influenza Spread between Human and Swine Populations using NAADSM*

* Dorjee, S., C. W. Revie, Z. Poljak, W. B. McNab and J. Sanchez, 2013: One-Health simulation modeling: A case study of influenza spread between human and swine populations using NAADSM. Transboundary and Emerging Diseases (Accepted).

3.1 Abstract

The circulation of zoonotic influenza A viruses including pH1N1 2009 and H5N1 continue to present a constant threat to animal and human populations. Recently an H3N2 variant has spread from pigs to humans and between humans in limited numbers. Accordingly, this research investigated a range of scenarios of the transmission dynamics of pH1N1 2009 virus at the swine-human interface while accounting for different percentages of swine workers initially immune. Furthermore, the feasibility of using North American Animal Disease Spread Model (NAADSM) applied as a one-health simulation model was assessed. The study population included 488 swine herds and 29,707 households-of-people within a county in Ontario, Canada. Households were categorized as: (i) rural households with swine workers, (ii) rural households without swine workers, and (iii) urban households without swine workers. Forty eight scenarios were investigated, based on the combination of six scenarios around the transmissibility of the virus at the interface and four vaccination coverage levels of swine workers (0% to 60%), all under two settings of either swine or human origin of the virus. Outcomes were assessed in terms of stochastic 'die-out' fraction, size and time to peak epidemic day, overall size and duration of the outbreaks. The modeled outcomes indicated that minimizing influenza transmissibility at the interface and targeted vaccination of swine workers had significant beneficial effects. Our results indicate that NAADSM can be used as a framework to model the spread and control of contagious zoonotic diseases among animal and human populations, under certain simplifying assumptions. Further

evaluation of the model is required. In addition to these specific findings, this study serves as a benchmark which can provide useful input to future one-health influenza modeling studies. Some pertinent information gaps were also identified. Enhanced surveillance and the collection of high quality information for more accurate parameterization of such models are encouraged.

Keywords: Modeling, one-health, zoonotic, influenza, zoonosis, pigs, humans, NAADSM.

3.2 Introduction

The on-going threat of an influenza pandemic emerging in people was highlighted with the novel pandemic H1N1 influenza virus (pH1N1) in 2009. The pH1N1 was first reported in March to April of 2009 in Mexico, and spread rapidly across the world (Centers for Disease Control and Prevention (CDC), 2009, Fraser et al., 2009, WHO, 2009). By 11 June 2009 a full scale pandemic was declared by the World Health Organization (WHO, 2009). Molecular analyses showed that the virus was genetically similar to contemporary viruses circulating in swine, based on livestock surveillance data in different continents (Garten et al., 2009, Smith et al., 2009). However, the origin of the virus and the exact host species involved in the reassortment remains unknown.

The first detection of pH1N1 in swine was reported from the province of Alberta, Canada in May of 2009 (OIE, 2009). It was introduced into the herd by an employee

(i.e. human-to-animal spread of pH1N1), who had recently returned from a vacation in Mexico (Howden et al., 2009). Swine-to-swine transmission of pH1N1 was subsequently demonstrated in several experimental (Itoh et al., 2009, Lange et al., 2009, Vincent et al., 2009, Brookes et al., 2010) and observational studies (Howden et al., 2009, Lange et al., 2009, Pasma and Joseph, 2010). By April of 2010, 20 different countries had reported outbreaks of pH1N1 in swine (Hofshagen et al., 2009, OIE, 2009-2010, Moreno et al., 2010, Pasma and Joseph, 2010, Pereda et al., 2010, Song et al., 2010, Sreta et al., 2010, Welsh et al., 2010, Forgie et al., 2011). Although the respective sources of many of these outbreaks remain unknown, some were confirmed (Norway, in addition to Canada), or were suspected (Finland, Iceland and Russia) of having involved human-to-swine transmission (Hofshagen et al., 2009, Howden et al., 2009, Forgie et al., 2011). In light of these reports of pH1N1 outbreaks in swine in several countries, it is surprising that no studies have reported either temporal or temporo-spatial spread of the virus between swine farms (Torremorell et al., 2012, Dorjee et al., 2013). Immediately after the reported outbreaks of pH1N1 in swine in Canada, restrictions on the export of live pigs and pork were imposed by several countries (Lynn, 2009, Reuters, 2009). Even without significant documented spread of pH1N1 from swine to humans, the social and economic consequences arising from the subsequent trade restrictions were devastating. Accordingly, zoonotic influenza A viruses are of interest to animal and public health authorities, given their significant implications for public health, animal health and trade.

Influenza pandemics remain a major zoonotic threat to mankind, occurring every one to four decades since 1918 (Brown, 2000, Ma et al., 2009, Zimmer and Burke, 2009). Since the first report of transmission of the H1N1 1918 virus from humans-to-pigs (Shope, 1931), the transmission of influenza A viruses back and forth between people and swine has been well documented (Hinshaw et al., 1978, Easterday, 1980, Dacso et al., 1984, Myers et al., 2007). There is much evidence of reassortments of swine, human and avian influenza viruses occurring in pigs in Europe (Brown et al., 1998) and in North America (Zhou et al., 1999, Karasin et al., 2000, Lekcharoensuk et al., 2006, Olsen et al., 2006). The transmission of influenza viruses from pigs to people has been reported in a number of studies (Brown, 2000, Myers et al., 2007, Robinson et al., 2007, Ma et al., 2009, Zimmer and Burke, 2009). Recently the transmission of the H3N2 variant from pigs-to-humans, and a subsequent limited spread between humans, was reported in the US (Lindstrom et al., 2012). Based on the findings of this study, swine should be considered potential hosts for the emergence of novel pandemic influenza strains. Cross-sectional serological studies found that those employed in occupations involving direct contact with pigs (e.g. swine-farmers, veterinarians, abattoir-workers) are at higher risk of zoonotic influenza infection. Swine farmers were relatively at higher risk than veterinarians and abattoir-workers (Olsen et al., 2002, Myers et al., 2006). The shift to large-scale swine operations involving frequent restocking of young susceptible pigs has facilitated the persistence of influenza viruses in herds (Vincent et al., 2008, Gray and Baker, 2011). The persistent transmission pressure between swine

and those working with pigs in commercial swine enterprises increases the opportunity for zoonotic spread of novel influenza viruses (Myers et al., 2006). This being the case, it is important to understand the transmission dynamics of influenza at the swine-human interface, to devise intervention strategies.

Recently, mathematical models and simulation tools have been developed to study the spread and control of influenza among human (Longini et al., 2004, Longini et al., 2005, Flahault et al., 2009, Gojovic et al., 2009) and avian (Le Menach et al., 2006, Guberti et al., 2007, Tiensin et al., 2007) populations. A small number of studies have investigated the spread of influenza from birds-to-birds and from birds-to-humans (Arino et al., 2007, Iwami et al., 2007, Kim et al., 2010), whereas to the best of our knowledge only one study investigated the spread of influenza within and between swine and human populations simultaneously (Saenz et al., 2006).

Given, (a) the impact of influenza on human health and the economy, (b) the importance of swine in the generation of novel influenza viruses, and (c) the utility of models in providing a better understanding of disease transmission and control dynamics; it is imperative to investigate key parameters influencing the spread and the effectiveness of mitigation strategies against influenza at the swine-human interface through simulating a range of possible scenarios. Such information can be used to guide the development of contingency measures to prevent and control the emergence of future influenza pandemics.

A number of computer software have been developed to implement models to assess the spread and control of highly contagious animal diseases, such as AusSpread (Garner and Beckett, 2005), InterSpread Plus (Stevenson et al., 2013) and NAADSM (Harvey et al., 2007, NAADSM Development Team, 2008). To date, these tools have been used to model single or multiple livestock species but have not attempted to incorporate spread between domestic animal and human populations. Most published models used to study spread of diseases among domestic livestock populations use the herd, rather than the individual animal, as the unit of interest. In contrast, most models used to study influenza spread among people use the individual, rather than the household or group of people as the unit of interest. However, a few studies in humans have investigated the spread and control of influenza at the individual household level (Wu et al., 2006, Fraser, 2007, Shaban et al., 2009). The NAADSM disease modeling framework was originally developed to accommodate different parameters of disease spread between different types of livestock herds or flocks (e.g. dairy cattle, vs. beef cattle, vs. swine, vs. sheep vs. goats in the spread of foot-and-mouth disease) (Harvey et al 2007). While the concept of using NAADSM to model households of people as a type of "herd" was not originally envisioned in development, it was subsequently proposed by McNab (McNab 2009, personal communication). This approach provided the opportunity to model the interface of the spread and control of zoonotic diseases within and between groups of animals and people under certain simplifying assumptions.

The overall objective of this study was to identify the relative importance of disease transmission parameters affecting the spread and control of contagious pathogens shared between people and swine, using influenza as an example. Specific objectives included: (i) investigation of the feasibility of using NAADSM as a tool to model the spread and control of zoonotic diseases; (ii) a study of the transmission dynamics of influenza at the swine-human interface using characteristics of pH1N1 as an example; and (iii) an investigation of the utility of applying targeted vaccination against influenza at the animal-human interface. We chose to use pH1N1 as our example of zoonotic pathogen due to the fact that: (i) it is easily transmissible between humans, swine, and human and swine populations, (ii) information about the biology of this virus is relatively abundant, and (iii) there were several questions arising from pH1N1 concerning its dynamics at the human-swine interface.

3.3 Materials and Methods

3.3.1 Study area and populations

A county within the province of Ontario, Canada, with a relatively high density of swine farms along with the existence of a range of rural and urban areas (one small city and four towns) was selected for this study. The following spatially explicit units were included as "production types" in the models: (i) swine herds (SH), (ii) rural households with at least one swine worker (SWH), (iii) rural households with no swine workers (RH), and (iv) urban households without swine workers (UH). Swine workers (owners/managers/labourers of swine farms) served as the bridging population for

pH1N1 transmission between swine and human populations. Population data to ensure a representative mixture of each type of unit within the model were extracted from the 2006 official census of Statistics Canada (Statistics Canada, 2007, Statistics Canada, 2007(b)). A total of 488 SH with 664,508 pigs were recorded in the census year of 2006 for the county. As only the aggregate number of SH and pigs were available at the census consolidated subdivision level, the number of animals per farm in the model was generated using a uniform distribution with minimum and maximum values of 500 and 2500 animals respectively (±4 standard deviation from a mean of ~1500 animals). The number of SWH was approximately 1.5 times the number of SH, based on the data for swine operators and agricultural laborers (a general figure not reported by enterprise type) recorded in the 2006 official census. A total of 25,297 people in 8,612 rural households were reported in this county. Therefore an appropriate number of RH (7,879) was generated by subtracting the number of SWH (733) from the total rural households. The numbers of UH and people recorded in the five urban areas were as follows: City A - 13,316 households with 30,461 people; Town B - 2,733 households with 6,617 people; Town C - 2,731 households with 6,303 people; Town D -1,714 households with 4,220 people; and Town E - 601 households with 1,446 people. A Poisson distribution with a mean of 3 and truncated at two and seven for SWH, and one and six for RH and UH were assumed for the number of people living in each household as per the census record. The final study population units and respective unit sizes are presented in Table 3.1.

3.3.2 Swine farm and household locations

Digital vector maps delineating the boundaries of rural and urban areas of this county were obtained from Statistics Canada (Statistics Canada, 2007(c), Statistics Canada, 2007(d)). Since the specific geographic coordinates of SH, SWH, and RH were not available in the official census data, their locations were randomly distributed spatially within the agricultural areas of the county using a Geographic Information System. A minimum distance of one kilometer was specified between swine herds. Swine-worker household locations of owners/managers and laborers were generated within the radii of 100-300 meters and 300-500 meters of SH respectively. Although some swine workers stay in towns, this was done to restrict the contact of a SWH to a specific farm for all iterations. This was achieved by also specifying the maximum contact distance between SWH and SH to 0.5 km. The RH locations were generated randomly in agricultural polygons with the additional constraint that they must be outside a 500 meters radius of any SH and at least a distance of 10 meters away from any other household. Similarly locations of UH were randomly distributed within the five urban boundaries, specifying a minimum distance of 10 meters between any two households. All spatial data manipulation and random spatial locations were generated using Quantum GIS (QGIS) version 6.1.0 (Open Source Geospatial Foundation Project. http://qgis.osgeo.org).

3.3.3 Model structure

3.3.3.1 North American Animal Disease Spread Model (NAADSM)

The supercomputer version of the NAADSM 3.1.24 (NAADSM Development Team, 2008) was used for the construction and simulation of models for pH1N1 spread in swine and human populations. The NAADSM is an agent-based platform that simulates the spread of diseases in populations using stochastic, spatially explicit, state-transition methods. The epidemiological unit of interest within NAADSM is an aggregation of animals managed together as a single unit at a single geographic location, typically as a herd or flock. The platform was developed to simulate the spread and control of contagious animal diseases (e.g. foot-and-mouth disease) between spatially explicit groups of animals, either of the same or different species and production types. It is flexible in the manner in which users can define the spread of a disease between different pairs of units (e.g. dairy cattle to beef cattle; swine farrowing operation to swine grower/finisher operations, etc.). It models disease transmission between farms by direct contact (through movement of live animals between farms), indirect contact (through the movement of people and contaminated fomites) as well as airborne and local area spread. The local area spread feature enables a user to specify other mechanisms of disease spread locally through insect pests, between animals of two adjacent farms across the fence and as a result of lapses in biosecurity measures. It has provisions to quantify the predicted number of infected premises arising from a number of different disease intervention strategies, such as quarantine and movement control,

vaccination, depopulation, and zoning. Each unit is initially assigned attribute data, including: a unique unit ID; the type of unit (e.g. dairy, beef, swine, etc.); number of animals in that unit; location of the unit (i.e. point geo-coordinates in longitude and latitude), and disease transition state. A detailed description of NAADSM has been provided by Harvey et al., (2007) and Hill and Reeves (2006).

3.3.3.2 Disease states

A susceptible-exposed-infectious-recovered (SEIR) model structure was used for each of the types of epidemiological units of interest described in this study (that is, SH, SWH, RH and UH). Susceptible units were herds or households susceptible to infection but not infected; exposed/latent units were those that had been infected but were not shedding the virus; infectious units were units shedding organisms; while recovered units were those that had recovered and were immune to further infection. The unit-level latent period was assumed equal to the time from the first individual within the unit became infected to the time when the first individual transited to the infectious state. The unit remained in the infectious state from the time when the first individual within the unit became infectious to the time until the last individual in that unit transited to the recovered state. Therefore, the unit-level latent period was equal to the duration of individual-level latent state, whereas a unit-level clinical infectious period varied with the size of the infected unit. Following infection, a susceptible unit transited through the subsequent disease states beginning on the day following infection in a cyclic fashion in the absence of any intervening control measures, such as vaccination or depopulation.

The duration of each of these disease states for any particular unit type was either based on a fixed value or was chosen stochastically from the defined probability distribution as described in the model parameters section below. Permanent immunity was simulated by setting a naturally immune duration which exceeded the duration of the simulated period (365 days).

3.3.3.3 Disease transmission

To investigate the transmission dynamics of pH1N1 between swine and human populations, its spread was simulated between different combinations of pairs of unit types as follows: (a) amongst swine herds (SH to SH), (b) between SH and SWH, and (c) amongst SWH, RH and UH, simultaneously. The influenza transmission among swine herds was simulated by both direct and indirect contacts, while the spread between SH and SWH, and amongst households occurred only through direct contact. A latently infected SH unit was also assumed infectious to other susceptible SH units by direct contact, as shipment of latently infected pigs to susceptible units would most likely result in transmission of infection. In all other cases only the infectious units could transmit the infection to the susceptible units. For the disease spread from SH to SWH and vice-versa, direct contacts were assumed to have occurred when the swine workers came in contact with pigs on farms (SH) during the course of their daily work. To ensure that each SWH was assigned to a specific farm throughout the simulation, a movement distance restriction zone of uniform distribution between 100–500 metres was created as per the synthetically generated locations of SWH described above.

For influenza spread amongst households, a direct contact was assumed to have occurred implicitly when an individual from an infectious household established contact with individuals from other households at any place, such as schools, workplaces or other areas where individuals congregate (not necessarily moving into recipient households in NAADSM context). Individuals who become newly infected as a result of contact with an infectious person outside their home could, in turn, infect infect individuals with their home and outside of their home. Similar assumptions have been made in modeling influenza spread at the household level (Wu et al., 2006, Fraser, 2007, Shaban et al., 2009). The influenza transmissions between infectious and susceptible units through direct and indirect contacts were simulated as a function of contact rate, the probability of infection per contact and movement distance distribution between the units.

3.3.4 Model parameters

3.3.4.1 Duration of disease states

Parameters for both the individual and unit level duration of the different disease states for swine and human populations are presented in Table 3.2 and 3.3 respectively. The individual level parameters for swine and human populations were extracted from the published literature (references are provided in tables). Since no information for clinical infectious period existed at the herd or household levels, they were generated from the individual-level parameters using the WithinHerd (WH-within herd disease spread model) software version 0.9.5 (Reeves et al., 2013). This is a stochastic modeling

framework that simulates the within-unit disease spread and generates the herd-level durations of disease states. The same swine and household populations were used for the within-unit influenza spread simulations. A BetaPERT distribution (which was the best fitting probability distribution of clinical infectious duration based on the output of the within-herd transmission model) based on the minimum, mode and maximum values of 100 iterations of the within-unit spread models of swine herd (except for latent period for which a fixed value of one day was assumed) or household populations were then used for NAADSM models. The durations of immunity period for SH and households were assumed to be permanent as is commonly the case in influenza modeling studies.

3.3.4.2 Contact frequencies

Daily direct and indirect contact frequencies among SH were extracted from the published and unpublished sources (Table 3.4). Data on how frequently pairs of different household population types contact each other were not available. Therefore, assumptions based on the informed judgement of the co-authors were made. These assumptions, along with the average daily individual contact frequency of 13.5, extracted from Mossong et al., (2008) and Lee et al., (2009), were used to derive the mean daily contact rate between different pairs of the population types (Table 4.4). As SWH and RH were in rural communities, only half the individual daily contact frequency noted above was used here. Co-authors also discussed and used their best judgement to specify the movement distance distributions between source and recipient units for all populations.

3.3.4.3 Disease transmission probabilities

In general, it is difficult to measure the transmission probability per contact and therefore it is mostly derived from calibrating models to match either the cumulative number of cases or R_0 (basic reproductive number defined as a number of average secondary cases produced by an infectious case during the infectious period in a totally susceptible population) of on-going or historical outbreaks (Saenz et al., 2006, Rahmandad and Sterman, 2008, Vynnycky and White, 2010). Given an R_0, a contact rate (C) and an average duration of infectiousness of totally susceptible individuals (D), transmission probability per contact (P- is the probability that an infection will be transferred between infected and susceptible units given an adequate contact) can be derived from the following formula (Saenz et al., 2006, Rahmandad and Sterman, 2008, Vynnycky and White, 2010):

$$R_0 = C * P * D$$

However, neither an estimate of R_0 nor historical data on influenza spread between farms were available in the literature. Therefore, for simplicity, transmission probabilities of 100% and 1% were assumed for direct and indirect contacts, respectively. In reality, all other parameters being equal, the transmission probability among units will vary depending on the within-unit prevalence and the number of animals shipped from infected to susceptible farms. These assumptions may not be unreasonable as within-herd spread of influenza in swine is known to be rapid and no immunity is anticipated to exist in naïve recipient herds to a novel strain such as pH1N1.

For spread amongst households, the transmission probability per contact (P) was estimated from individual level data using the formula provided above. Based on the minimum, most likely and maximum R_0 values of 1.3, 1.5, and 2.2 respectively (Fraser et al., 2009, Pourbohloul et al., 2009, Tuite et al., 2010), corresponding daily contact frequencies of 6.9, 13.1, and 18.2 (Mossong et al., 2008), and the duration of infectious period of 2, 7, and 10 days respectively (Pourbohloul et al., 2009, Yang et al., 2009), the mean and 95% confidence interval (CI) of the transmission probability was estimated using a Monte Carlo simulation of 1,000 iterations in PopTool version 3.2.5 (Microsoft Excel add-in program available at www.poptools.org). The mean of 0.024 (95% CI 0.012–0.048) of the transmission probability per contact was obtained. This estimate was not dissimilar to the median value of 0.043 used by Lee et al. (2009).

Other general assumptions made within the model were as follows: all swine and human populations were totally susceptible to the virus, all populations were closed with no addition or losses throughout the simulation period (as the mortality of pigs from pH1N1 is negligible [OIE, 2009], and pH1N1 mortality in humans is less than 1%); populations were homogeneous with mixing (both direct and indirect contacts) both within and between groups based on spatial probability kernel (that is units near the infectious unit have a higher probability of contact) and as defined by the contact structures. In addition, the disease spread through direct or indirect contacts between our study populations and similar populations of other counties in the province were not considered.

3.3.5 Scenarios

The transmission dynamics and the extent of spread of pH1N1 both within and between swine and human populations were assessed under the two broad scenarios of the virus origin, from a swine herd or from urban households. Within each of these broad scenarios the speed, duration and magnitude of the disease spread were investigated at three different levels of the transmissibility (low, medium and high) at the swine-human interface. Six possible combinations of transmissibility of the virus at the swine-human interface were investigated; (i) low animal to human - low human to animal (LL), (ii) medium animal to human - low human to animal (ML), and so forth, as summarized in Figure 3.1. The values used for low (low animal to human or low human to animal) and high (high animal to human or high human to animal) transmissibility were equal to those estimated for human to human spread (P = 0.024) and swine to swine spread (P = 1.0), respectively. A medium transmissibility (medium animal to human or medium human to animal) of P = 0.3 was used based on the higher value suggested by Lee et al. (2009).

Each of these scenarios was investigated at four levels of initially immune SHW population (0%, 15%, 30%, and 60%). It was assumed that all members of the SHW family have been vaccinated and was 100% immune to the infection throughout each simulated outbreak. It was based on the assumption that a limited stockpile of effective vaccine was available at the very early phase of an outbreak and assessing the benefit of targeted vaccination of SWH population. A total of 48 scenarios was investigated in

assessing the transmission dynamics at the swine-human interface (Figure 3.1). In the case where the virus originated in swine herd the infection was seeded into a single randomly selected SH for all iterations. For the scenario of virus originating in human population it was seeded in five randomly selected UH for all iterations. Each scenario was simulated over 1,000 iterations in time-steps of one-day for 365 days.

3.3.6 Statistical analyses

The models' outcomes were assessed in terms of the parameters that were relevant from epidemiological and regulatory perspectives. They included: (i) stochastic 'die-out' fraction - proportion of iterations that did not result in an epidemic outbreak; defined as <1% of units (total populations combined) becoming infected, (ii) time to peak epidemic day - day on which a highest number of infectious units was observed, (iii) epidemic size on peak day - number of infectious units observed on the peak epidemic day, (iv) outbreak duration - time to-end-of an outbreak, defined as the time until no latent or infectious unit was present, or a cut-off value of 365 days if the outbreak persisted beyond the simulated time period, and (v) outbreak size - total number of infected units. Summary statistics associated with these outcomes (5^{th}, 50^{th} and 95^{th} percentiles of 1,000 iterations) were generated for all scenarios. The cut-point of <1% of units infected was chosen to define the 'stochastic die-out' fraction as the percentage of units infected was >30% in all other iterations. The effects of the three parameters; (i) origin of the virus, (ii) transmissibility of the virus at the swine-human interface, and (iii) vaccination of SWH on the outbreak duration and proportion of units infected were evaluated by

fitting the survival and binomial logistic regression models, respectively. Fitting the multivariable models allowed for an assessment of interaction effects between these parameters on the outcomes.

An accelerated failure-time (AFT) survival model (using the generalized linear model (glm) function with a gamma distribution) was fitted to the epidemic duration as the outcome variable, and the three input parameters as predictor variables. All iterations were considered failed event at the end of the outbreak duration. All input parameters were coded as categorical variables. The origin of the virus was coded as 1 = swine origin (reference category) and 2 = human origin. The transmissibility of the virus at the interface was coded as 1 = LL (reference category), 2 = ML, 3 = HL, 4 = MM, 5 = HM, and 6 = HH. The vaccination coverage of SWH was coded as 1 = 0% (reference category), 2 = 15%, 3 = 30%, and 4 = 60%. All 2-way interactions among the predictors were evaluated and retained if significant at $P < 0.05$ and if the relative difference in the predicted duration of epidemic at any levels of the interaction terms was greater than one-week duration. This criterion was used since even a small difference between two interaction terms tended to exhibit statistical significance due to large sample size (each scenario being simulated 1,000 times). Akaike Information Criterion (AIC) and Cox-Snell residual plots were used to select the best fitting AFT parametric survival model as well as to evaluate the overall fit of the model to the data (Dohoo et al., 2009). Residuals were evaluated using deviance residual and plotting the residuals against the fitted values or individual predictors.

The effect of the predictors on the size of epidemic was assessed using logistic regression for binomial data (glm function with binomial family distribution and logit link). All predictors were entered into the model as described in the survival model above. The number of each population type infected in each scenario was combined together into single outcome variable, and a variable of the population type was generated. This variable was coded as 1 = SH, 2 = SWH, 3 = RH, and 4 = UH. This allowed assessing the effects of the predictors on epidemic size for each of the population type using a single model. All two-way interactions among the predictors were examined and retained if they were significant at $P< 0.05$ and, if the relative difference in the predicted proportion of units infected at any levels of the interaction terms was ≥5%. Model diagnostics and residuals were evaluated based on the deviance chi-squared test and deviance residuals. Results of the survival and the binomial logistic regression models are presented in terms of predicted margins of median epidemic duration and proportion of units infected at the representative values of the covariates. All analyses were implemented in Stata version 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

3.4 Results

3.4.1 Stochastic 'die-out' fraction

The stochastic nature of the modeling approach used in this study was reflected not only in the variability of the predicted measures, but also by the probability of an infection dying out without leading to an outbreak, by chance alone. We observed that 5% of the

24,000 iterations (equivalent to the number of simulated influenza outbreaks) underwent stochastic 'die-out' when the virus originated in swine. Furthermore, the majority of the 'die-out' iterations (59%) were observed when the transmissibility of the virus at the swine-human interface was low (LL scenario); followed by iterations involving 60% vaccination coverage of SWH (42%) (Figure 3.2). No such 'die-out' was observed when the infection was seeded into five randomly selected UH (human origin of the virus).

3.4.2 Peak epidemic day and size

It took approximately 25 days to infect the first UH in the case of the virus originating in swine population, whereas it took approximately 45 days to infect the first SH when the virus originated in the human population. The time to reach the peak epidemic day and the epidemic size of the peak day were estimated as the median of 1,000 iterations for each scenario. In general, the delay to peak epidemic day was shorter and the epidemic sizes of the peak days were higher as the transmissibility of the virus at the swine-human interface increased. In contrast, as the vaccination coverage of SWH increased the delay to peak epidemic day was longer and the epidemic sizes of the peak days were smaller in both swine herd and household populations.

As the origin of the virus, was directly correlated with delay to the peak epidemic day and the epidemic size of the peak day in the corresponding swine herd or household populations, respectively, we focused our attention on the effects of the transmissibility of the virus and vaccination parameters on these outcome measures to the UH origin for SH population, and SH origin for the household populations. In the case of SH, the

higher transmissibility of the virus (MM to HH) significantly shortened the delay to peak epidemic day by 3–5 weeks (15–26% reduction) compared with low transmissibility (LL to HL) across all levels of vaccination coverage (Figure 3.3). The delays to the peak epidemic days among LL to HL or MM to HH were practically small (difference of approximately less than one week i.e. <8% reduction). The differences in the epidemic sizes of the peak days amongst different scenarios of the transmissibility of the virus at the interface were small (a difference of ≤4 infected units) across all levels of the vaccination coverage.

Vaccinating 60% of SWH delayed the peak epidemic day by 2–3 weeks (14–20% longer) compared with the scenario with no vaccination, in the SH population across all levels of the transmissibility (Figure 3.3). However, the vaccination coverage up to 30% had only a small effect (<7% increase in the time to peak epidemic day). The differences in the epidemic sizes of peak days amongst various vaccination coverage levels were small (a difference of ≤4 infected units).

In the household populations, the delay to peak epidemic day was longer by approximately 3–6 weeks (15–31% longer) when the transmissibility of the virus at the interface was low (LL) compared with the higher transmissibility (ML to HH) across all levels of the vaccination (Figure 3.4). This effect was more apparent in the scenario with no vaccination. The epidemic size of peak day was lower by 11–22 infected households (a moderate reduction of 7–15%) when the transmissibility of the virus was low (LL) than at the higher transmissibility levels (ML to HH).

Vaccinating 60% of the SWH delayed the peak epidemic day by 2–5 weeks (13–33% longer) and reduced the epidemic size on the peak day by 33–37 infected households (a moderate reduction of 20–22%) compared with no vaccination scenario. However, the effects of 15% to 30% vaccination coverage on these two outcomes measures were small (<12% change on the delay time and the epidemic sizes of the peak days).

3.4.3 Epidemic duration

The overall median (5^{th} and 95^{th} percentiles) epidemic duration was 308 (261–365) days. The result of the survival model on the epidemic duration indicated that an AFT model with gamma distribution fitted the data best. All the predictors (that is input parameters from the scenarios) had a significant effect on the epidemic duration. The only significant interaction observed was between the transmissibility of the virus and the proportion of SWH vaccinated. The predicted median epidemic duration was 6 days longer in the case where the virus originated in swine than in humans, at all levels of the transmissibility and the vaccination coverage. Though statistically significant, this difference was too small to be considered practically meaningful. The interaction effect between the transmissibility and vaccination was mainly due to the significant change in the slope (shortening of the epidemic duration) between low (LL) versus the higher transmissibility (ML to HH) at the low vaccination coverage (0% to 30%) (Figure 3.5). This means under low vaccination coverage the increase in the transmissibility of the virus (LL vs. ML to HH) will shorten the epidemic duration relatively more (3–6% reduction) compared with the vaccination coverage of 60% (1–3% reduction).

The deviance residuals did not indicate any particular outlying observation, except for the stochastic 'die-out' fraction (1,188 iterations). Excluding these iterations increased the predicted median epidemic duration up to 7% for the origin of the virus and for the interaction term between the transmissibility and vaccination coverage.

3.4.4 Epidemic size

The overall median (5^{th}–95^{th} percentiles) of infected units were 83% (67–98%) of SH, 69% (34–99%) of SWH, 54% (47–58%) of RH, and 35% (34–36%) of UH. The logistic regression results showed that the effect of the transmissibility and the targeted vaccination of SWH on the epidemic size depended (significant interaction) on the population types (Figure 3.6). Furthermore, the interaction effect between the transmissibility and the vaccination on the epidemic size was significant. The proportion of SH infected was significantly higher when the transmissibility of the virus from human to animal was higher (MM to HH) compared to when it was low (LL to ML) (Figure 3.6 (a)). However, the magnitude of the difference was relatively larger (by 9–13%) at vaccination coverage of 60% compared with coverage of 0–30%. While the vaccination coverage up to 30% caused a small reduction (1–8%) in the proportion of SH infected, 60% coverage had significant reduction (8–21%), particularly at the low transmissibility of the virus from human to animal spread (LL to ML) (19–21% reduction).

For the SWH units, a significant difference in the proportion of SWH infected was observed between the low (LL) versus higher transmissibility (ML to HH) of the virus

(Figure 3.6 (b)). Furthermore, this difference was relatively larger when SWH were vaccinated (15% to 60%) compared to no vaccination, a difference of 12–17% vs. 4–5% respectively. Similarly vaccination reduced the proportion of SWH infected by 13–68%, with relatively larger reduction at the low transmissibility of the virus (LL). While the vaccination caused a small reduction in the percentage of RH infected (up to 9% reduction), the transmissibility of the virus had negligible effect on the proportion of RH and UH infected (Figure 3.6 (c) and (d)).

The overall goodness-of-fit test of the final model using deviance chi-squared test showed a significant lack of fit ($P<0.001$) with a deviance over-dispersion parameter of 197.9. Most observations with extreme deviance residuals were the stochastic 'die-out' fraction. Excluding these observations improved the fit of the model substantially (a deviance over-dispersion parameter of 4.87). However, 18% of the iterations still had deviance residuals greater than or less than ±3. These residuals were spread over all covariate patterns and were related to the stochastic variability in the outcome within the same covariate pattern. In contrast to statistical modeling of risk factors, the proportion of ill-fitting residuals from the predicted outputs actually provides insight into stochastic variability in the predicted outcome by chance alone. Since there was no reason to exclude these observations associated with the stochastic 'die-out' fraction, the results using the full dataset were reported.

3.5 Discussion

Several questions related to the transmission dynamics of zoonotic influenza viruses at the swine-human interface have recently been raised by infectious disease control authorities around the world, including the potential benefit of targeted vaccination of swine workers. To address these questions, in this study we investigated the transmission dynamics of pH1N1 2009 virus between swine and human populations by modeling its spread amongst and between swine and human populations simultaneously. Furthermore, the benefit of vaccinating varying proportions of SWH was assessed. To our knowledge (Dorjee et al., 2013) only a single study has modeled the spread of zoonotic influenza between swine and human populations simultaneously (Saenz et al., 2006). Our approach differs from that of Saenz et al., (2006) in a number of ways. Most importantly: (a) this is a stochastic, spatially explicit agent-based model with the unit of simulation being the farm or household, while the previous study used an aggregate deterministic model with homogeneous mixing, (b) we categorized the non-swine worker human population into a mix of rural and urban households, (c) we assessed the effect of different levels of transmissibility of the virus at the swine-human interface, while the previous model investigated the amplifying effect of the influenza spread in rural population by swine and swine worker populations. It should be noted that the emphasis of our study involved a qualitative investigation of the effects of different scenarios (input parameters) rather than on any perceived accuracy of quantitative predictions.

The 5% stochastic 'die-out' fraction observed in cases of a single infection seeded into the SH population indicates a fraction of outbreaks that can be expected to undergo random extinction without causing an outbreak of epidemic proportion, given the assumptions inherent in this model. The fact that the majority of this fraction was observed in cases that assumed low transmissibility of the virus at the interface (LL) and/or where 60% of the SWH were vaccinated, indicates the beneficial effect of lowering the transmissibility of the virus or of achieving high coverage of targeted vaccination as a means of preventing a proportion of outbreaks. Although, the magnitude of this effect will be affected by the location of the index premise and the density of the populations surrounding it, we would expect to observe such phenomena in real-world situations. The extent to which such location-specific effects might be a factor could not be ascertained due to the fact that the current version of the NAADSM lacks the ability to randomly seed infections at different locations for each iteration.

The significant difference between the scenarios of low (LL to ML) versus medium to high (MM to HH) transmissibility of the virus from humans to animals in terms of all outcome measures in SH population indicated that the spread of the virus from humans to animals had a larger impact than the animal to human spread. To a large extent this was due to higher contact rate between SH and SWH than between SH units. This result suggested that if we are to obtain a significant and positive beneficial effect on the outcome measures we should reduce the transmissibility of the virus from humans to animals to this low level. Reducing it to the low level would significantly prolong the

time to peak epidemic, lower the epidemic size of the peak day, as well as the overall outbreak size in the SH population. Similar significant beneficial effects of lowering the transmissibility of the virus at the interface would be obtained even in the household population. However, the transmissibility of the virus both from animals to humans and vice-versa had to be reduced to the low level (LL). The lowering of the transmissibility of the virus to the LL level also had the beneficial effect of reducing the overall size of the epidemic in SWH population. The positive implication of delaying the time to peak epidemic day is that veterinary and public health authorities would be provided with more time to mobilize resources and implement appropriate disease response measures, such as the delivery of antivirals, vaccination, or other social distancing measures. Furthermore, reducing the epidemic size on the peak day should reduce the burden of disease control activities (such as movement control and vaccination in animals) including the burden on health care facilities.

An important finding of this study is that it highlights the crucial role the transmission dynamics of influenza at the swine-human interface can play in influenza spread between swine and human populations. It indicated that opportunities exist to prevent or minimize the outbreak of zoonotic influenza by lowering the transmissibility of the virus at this interface. Transmissibility of the virus at the swine-human interface can be minimized through various mechanisms, including the following: good personal hygiene, avoiding direct contacts with sick pigs, using appropriate face masks (e.g. N95 respirator mask) and gloves, and not smoking while working with pigs (Ramirez et al.,

2006), instructing swine-workers to stay away from work when suffering from influenza like illnesses, and following strict farm biosecurity measures. As significant differences in the outcome measures were observed between low and medium to high levels of the transmissibility, further sensitivity analysis needs to be carried out between low and medium range of values to determine the threshold level at which a significant beneficial impact can be achieved. It is recommended that studies are carried out to quantify the percentage reduction in infection achieved through these important preventive measures at the swine-human interface to improve the parameterization of future modeling studies.

The transmissibility of the virus at the swine–human interface had little or negligible impact on the epidemic size in the RH and UH populations. This might suggest that once the infection has been introduced in the rural or urban populations it would spread in these populations independent of its spread at the swine-human interface, given the relatively larger population sizes and higher contact rates.

Significant beneficial effects on all the outcome measures were observed as the level of targeted vaccination of SWH increased, though the most significant changes were observed when 60% coverage was reached. These effects were most evident in the SH and SWH populations and to a lesser extent in the RH population. Its effect was negligible on the proportion of UHs infected, likely for similar reasons to those mentioned for the transmissibility above. Within the model, we assumed that an effective vaccine was available prior to the influenza outbreak. Questions still remain as

to whether such a vaccine would be readily available during the emergent phase of a novel virus. However, if a limited amount of such vaccine were to be available early on in an outbreak, targeting swine workers in cases where the virus was of swine origin should prove beneficial. Future work could investigate the effect of vaccinating similar proportions of the rural and/or urban populations.

3.5.1 Issues and information gaps associated with this modeling approach

In common with other modeling studies in this domain, a number of simplifying assumptions were made. For example, all populations were considered static and closed (that is we assumed no addition or removal of farms or households occurs during the simulation, and unit sizes are fixed throughout the simulation), and all populations were 100% susceptible to the influenza virus. Furthermore, contacts between populations of the county being modeled and neighbouring counties were ignored, which is not realistic as some movements of infected and susceptible populations between counties would be expected. Another simplifying assumption made was that once a single individual on a farm or in a household become infectious, that farm or household itself was infectious. This is an inherent assumption inbuilt into NAADSM Version 3.1.24. In reality all animals on a farm or individuals in a household may not become infected, though studies have shown that the large majority of animals do become infected during influenza outbreaks in farms (Howden et al., 2009, OIE, 2009-2010, Pasma and Joseph, 2010). Even the household secondary attack rates for pH1N1 were estimated in the range of 13% to 50% (Cauchemez et al., 2009, Ghani et al., 2009, Yang et al., 2009, van

Gemert et al., 2011). The probability of transmission is likely to be influenced by the within-farm or within-household prevalence of disease, but this effect was not accounted-for in the current study. Furthermore, the effect of animal shipment size on the transmission probability for direct contacts between SH units was not considered. In reality we would expect the transmission to be influenced by both within-farm prevalence and shipment size.

For simplicity all swine farms were treated as a homogeneous population; in reality epidemic size and length of disease outbreak will likely vary by farm type (farrowing, grower, finishing, etc.) as has been observed for classical swine fever (Dürr et al., 2013). Similarly, in human populations an individual's susceptibility to influenza viruses, including pH1N1, will vary by age and family size (Cauchemez et al., 2009, Yang et al., 2009, van Gemert et al., 2011). Other occupational groups such as veterinarians, abattoir workers, and swine transporters, who come into contact with swine, may play an important role in influenza spread but these groups were not considered in this study.

Information on how long a household would remain infectious was not available. However, deriving the period of household infectiousness from the individual data using the methods within NAADSM seems a reasonable approach. Furthermore, information on contact frequencies between SWH, RH and UH were not available with assumptions being based on the informed judgement of co-authors, which may have introduced some bias in the estimates. Due to time constraints, extensive sensitivity analysis to examine

the effects of all these parameters on the modeled spread of the virus was not carried out.

Despite reports of several outbreaks of pH1N1 across the globe in both human and swine populations, and the heightened interest in gaining a better understanding of the transmission dynamics involved at the swine-human interface, only one study was found that reported transmission back from pigs to humans (Howden et al., 2009). Although, it can be difficult to determine the direction and quantify the transmission of pH1N1 spread between humans and swine, it would be useful to carry out some prospective studies of transmission to generate key modeling parameters. Furthermore, no study could be found that reported the transmission of pH1N1 from one farm to another, either through direct shipment of animals or indirect contact (through movement of swine workers, veterinarians, and other fomites). More representative studies to estimate different stages of pH1N1 or other influenza virus infection at the farm level may provide useful information to parameterize models in the future.

3.5.2 Feasibility of NAADSM for zoonotic disease modeling

Observations from this study suggest that NAADSM provides a feasible platform for modeling directly transmitted contagious zoonotic diseases between animal and human populations under simplifying assumptions similar to those adopted in this study. NAADSM provides a sophisticated, flexible and user-friendly software platform. It is particularly useful to people with a biology background who do not possess strong mathematical or computer programming skills (as are typically required to make

appropriate use of other modeling software). Building model structures and specifying parameters relating to transmission and control strategies can be easily achieved within NAADSM as it requires only the specification of parameter values in the form of fixed values, probability density functions or relational functions. The software also has features to generate graphs, summary statistics, and to compare outcomes across as a range of different scenarios. In addition, NAADSM has features to assess all key intervention strategies either alone or in combination. These are relevant from a regulatory perspective, but are equally applicable to exploring issues relating to the public health.

One of the main constraints of using NAADSM for zoonotic disease modeling in animal and human populations simultaneously is that its unit of simulation has to be the household level. However, some of the studies mentioned above also emphasized the practicality of implementing control measures at the household rather than on an individual level in human populations. Nevertheless, good quality information on the natural history of influenza infection, its spread, contact rates at the household level are required to parameterize a model. For this purpose, a work similar to that reported by van Gemert et al., (2011) would be useful. The NAADSM does not have the flexibility to incorporate heterogeneity within a unit for parameters such as the contact rates, risk or susceptibility to a zoonotic agent that may vary significantly according to social demographics such as age or sex. Such heterogeneity is often an important component in models of human disease spread. It is also not possible to assign more than a single

location for each unit, in contrast to many human disease spread models where individuals can be assigned to two or more locations, such as the home, school/workplace, community or other places of social gathering. The NAADSM simulates the disease spread based not only on the contact rate and transmission probabilities, but also as a function of spatial distance between source and recipient units. However, households or people even in close geographic proximity may not have any contact between one another to facilitate influenza spread. Spatial location becomes largely irrelevant unless a disease spreads locally through aerosol transmission. There is currently no option in NAADSM to exclude spatial contact distance from being a key element of disease spread. This study addressed the issue to some extent by specifying larger spatial distances of contact between the units and assuming homogenous mixing between units within the specified distance. The NAADSM version used in this study lacks the capability to seed the infection in a population randomly for each iteration of the scenario. Even though each scenario was simulated for 1,000 iterations it did not capture the variability expected due to random seeding of infection in a population at different locations. It would be expected that the speed and extent of spread including stochastic 'die-out' fraction would be influenced to a certain extent by the density of population around the index unit. Despite these limitations, the stochastic modeling approach which NAADSM supports can be considered relatively superior to simple deterministic homogeneous and perfect mixing models. A major limitation of the personal computer version of the NAADSM observed is the time taken to simulate

populations of a significant size. Despite being run on a powerful Windows-based machine the 100 iterations of this study population with 30,195 units took around 4 days to complete.

3.6 Conclusion

In conclusion, this is a unique one-health modeling study which investigated the simultaneous spread of pH1N1 both within and between swine and human populations. It provided useful insights into how manipulating the transmission dynamics of pH1N1 at the swine-human interface can alter the spread of an influenza epidemic in swine and/or human populations, and illustrated the beneficial effects of targeted vaccination of swine workers. Minimizing transmissibility at the swine-human interface through appropriate mechanisms including targeted vaccination should form key components of all pandemic contingency measures for zoonotic influenza. The effect of preemptive targeted vaccination of swine workers seems useful as opposed to reactive 3 km ring vaccination of animals and people (Chapter 4). This study also serves as a benchmark for future studies to improve the modeling approaches of zoonotic influenza including other directly transmitted zoonotic diseases further through enhanced surveillance and collection of quality information to parameterize models accurately. This study also illustrated that the NAADSM is a feasible and relatively flexible platform for modeling a spread of directly transmitted zoonotic influenza between swine and human populations under certain simplifying assumptions.

3.7 References

Arino, J., R. Jordan and P. van den Driessche, 2007: Quarantine in a multi-species epidemic model with spatial dynamics. Math. Biosci., 206, 46-60.

Bates, T. W., M. C. Thurmond and T. E. Carpenter, 2001: Direct and indirect contact rates among beef, dairy, goat, sheep, and swine herds in three California counties, with reference to control of potential foot-and-mouth disease transmission. Am. J. Vet. Res., 62, 1121-1129.

Blaskovic, D., V. Rathova, R. Skoda, D. Kociskova and M. M. Kaplan, 1970: Experimental infection of weanling pigs with A-swine influenza virus. 1. Epidemiology and serological Response. Bull. World Health Organ., 42, 757-765.

Boëlle, P. Y., P. Bernillon and J. C. Desenclos, 2009: A preliminary estimation of the reproduction ratio for new influenza A(H1N1) from the outbreak in Mexico, March-April 2009. Euro Surveill., 14, pii=19205.

Brookes, S. M., A. Nunez, B. Choudhury, M. Matrosovich, S. C. Essen, D. Clifford, M. J. Slomka, G. Kuntz-Simon, F. Garcon, B. Nash, A. Hanna, P. M. Heegaard, S. Queguiner, C. Chiapponi, M. Bublot, J. M. Garcia, R. Gardner, E. Foni, W. Loeffen, L. Larsen, K. Van Reeth, J. Banks, R. M. Irvine and I. H. Brown, 2010: Replication, pathogenesis and transmission of pandemic (H1N1) 2009 virus in non-immune pigs. PLoS One, 5, e9068. doi:9010.1371/journal.pone.0009068.

Brown, I. H., 2000: The epidemiology and evolution of influenza viruses in pigs. Vet. Microbiol., 74, 29-46.

Brown, I. H., P. A. Harris, J. W. McCauley and D. J. Alexander, 1998: Multiple genetic reassortment of avian and human influenza A viruses in European pigs, resulting in the emergence of an H1N2 virus of novel genotype. J. Gen. Virol., 79, pt. 12, 2947-2955.

Cauchemez, S., C. A. Donnelly, C. Reed, A. C. Ghani, C. Fraser, C. K. Kent, L. Finelli and N. M. Ferguson, 2009: Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. N. Engl. J. Med., 361, 2619-2627.

Centers for Disease Control and Prevention (CDC), 2009: Swine influenza A (H1N1) infection in two children--Southern California, March-April 2009. MMWR. Morb. Mortal. Wkly. Rep., 58, 400-402.

Christensen, J., B. McNab, H. Stryhn, I. Dohoo, D. Hurnik and J. Kellar, 2008: Description of empirical movement data from Canadian swine herds with an application to a disease spread simulation model. Prev. Vet. Med., 83, 170-185.

Dacso, C. C., R. B. Couch, H. R. Six, J. F. Young, J. M. Quarles and J. A. Kasel, 1984: Sporadic occurrence of zoonotic swine influenza virus infections. J. Clin. Microbiol., 20, 833-835.

Desrosiers, R., R. Boutin and A. Broes, 2004: Persistence of antibodies after natural infection with swine influenza virus and epidemiology of the infection in a herd previously considered influenza- negative. J. Swine Health Prod., 12, 78–81.

Dohoo, I., W. Martin and H. Stryhn, 2009: Veterinary epidemiologic research, 2 edn. VER Inc., Charlottetown, PEI, Canada.

Dorjee, S., Z. Poljak, C. W. Revie, J. Bridgland, B. McNab, E. Leger and J. Sanchez, 2013: A review of simulation modelling approaches used for the spread of zoonotic influenza viruses in animal and human populations. Zoonoses Public Health, 60, 383-411.

Dürr, S., H. zu Dohna, E. Di Labio, T. E. Carpenter and M. G. Doherr, 2013: Evaluation of control and surveillance strategies for classical swine fever using a simulation model. Prev. Vet. Med., 108, 73-84.

Easterday, B. C., 1980: The epidemiology and ecology of swine influenza as a zoonotic disease. Comp. Immunol. Microbiol. Infect. Dis., 3, 105-109.

Flahault, A., E. Vergu and P. Y. Boelle, 2009: Potential for a global dynamic of Influenza A (H1N1). BMC Infect. Dis., 9, 129.

Forgie, S. E., J. Keenliside, C. Wilkinson, R. Webby, P. Lu, O. Sorensen, K. Fonseca, S. Barman, A. Rubrum, E. Stigger, T. J. Marrie, F. Marshall, D. W. Spady, J. Hu, M. Loeb, M. L. Russell and L. A. Babiuk, 2011: Swine outbreak of pandemic influenza A virus on a Canadian research farm supports human-to-swine transmission. Clin. Infect. Dis., 52, 10-18.

Fraser, C., 2007: Estimating individual and household reproduction numbers in an emerging epidemic. PLoS One, 2, e758.

Fraser, C., C. A. Donnelly, S. Cauchemez, W. P. Hanage, M. D. Van Kerkhove, T. D. i. Hollingsworth, J. Griffin, R. F. Baggaley, H. E. Jenkins, E. J. Lyons, T. Jombart, W. R. Hinsley, N. C. Grassly, F. Balloux, A. C. Ghani, N. M. Ferguson, A. Rambaut, O. G. Pybus, H. Lopez-Gatell, C. M. Alpuche-Aranda, I. B. Chapela, E. P. Zavala, D. M. E. Guevara, F. Checchi, E. Garcia, S. Hugonnet and C. Roth, 2009: Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings. Science, 324, 1557-1561.

Garner, M. G. and S. D. Beckett, 2005: Modelling the spread of foot-and-mouth disease in Australia. Aust. Vet. J., 83, 758-766.

Garten, R. J., C. T. Davis, C. A. Russell, B. Shu, S. Lindstrom, A. Balish, W. M. Sessions, X. Xu, E. Skepner, V. Deyde, M. Okomo-Adhiambo, L. Gubareva, J. Barnes, C. B. Smith, S. L. Emery, M. J. Hillman, P. Rivailler, J. Smagala, M. de

Graaf, D. F. Burke, R. A. M. Fouchier, C. Pappas, C. M. Alpuche-Aranda, H. Lopez-Gatell, H. Olivera, I. Lopez, C. A. Myers, D. Faix, P. J. Blair, C. Yu, K. M. Keene, P. D. Dotson, Jr., D. Boxrud, A. R. Sambol, S. H. Abid, K. St. George, T. Bannerman, A. L. Moore, D. J. Stringer, P. Blevins, G. J. Demmler-Harrison, M. Ginsberg, P. Kriner, S. Waterman, S. Smole, H. F. Guevara, E. A. Belongia, P. A. Clark, S. T. Beatrice, R. Donis, J. Katz, L. Finelli, C. B. Bridges, M. Shaw, D. B. Jernigan, T. M. Uyeki, D. J. Smith, A. I. Klimov and N. J. Cox, 2009: Antigenic and Genetic Characteristics of Swine-Origin 2009 A(H1N1) Influenza Viruses Circulating in Humans. Science, 325, 197-201.

Ghani, A., M. Baguelin, J. Griffin, S. Flasche, A. J. van Hoek, S. Cauchemez, C. Donnelly, C. Robertson, M. White, J. Truscott, C. Fraser, T. Garske, P. White, S. Leach, I. Hall, H. Jenkins, N. Ferguson and B. Cooper, 2009: The Early Transmission Dynamics of H1N1pdm Influenza in the United Kingdom. PLoS Curr., 1, RRN1130.

Gojovic, M. Z., B. Sander, D. Fisman, M. D. Krahn and C. T. Bauch, 2009: Modelling mitigation strategies for pandemic (H1N1) 2009. Can. Med. Assoc. J., 181, 673-680.

Gray, G. C. and W. S. Baker, 2011: Editorial commentary: the problem with pigs: it's not about bacon. Clin. Infect. Dis., 52, 19-22.

Guberti, V., M. Scremin, L. Busani, L. Bonfanti and C. Terregino, 2007: A simulation model for low-pathogenicity avian influenza viruses in dabbling ducks in Europe. Avian Dis., 51, 275-278.

Harvey, N., A. Reeves, M. A. Schoenbaum, F. J. Zagmutt-Vergara, C. Dube, A. E. Hill, B. A. Corso, W. B. McNab, C. I. Cartwright and M. D. Salman, 2007: The North American Animal Disease Spread Model: a simulation model to assist decision making in evaluating animal disease incursions. Prev. Vet. Med., 82, 176-197.

Hill, A. and A. Reeves, 2006: User's Guide for the North American Animal Disease Spread Model, 2nd edn. Fort Collins, Colorado: Animal Population Health Institute, Colorado State University. Available at http://www.naadsm.org.

Hinshaw, V. S., J. Bean Jr., R. G. Webster and B. C. Easterday, 1978: The prevalence of infuenza viruses in swine and the antigenic and genetic relatedness of infuenza viruses from man to swine. Virology, 84, 51- 62.

Hofshagen, M., B. Gjerset, C. Er, A. Tarpai, E. Brun, B. Dannevig, T. Bruheim, I. G. Fostad, B. Iversen, O. Hungnes and B. Lium, 2009: Pandemic influenza A(H1N1)v: human to pig transmission in Norway? Euro Surveill., 14.

Howden, K. J., E. J. Brockhoff, F. D. Caya, L. J. McLeod, M. Lavoie, J. D. Ing, J. M. Bystrom, S. Alexandersen, J. M. Pasick, Y. Berhane, M. E. Morrison, J. M. Keenliside, S. Laurendeau and E. B. Rohonczy, 2009: An investigation into

human pandemic influenza virus (H1N1) 2009 on an Alberta swine farm. Can. Vet. J., 50, 1153-1161.

Itoh, Y., K. Shinya, M. Kiso, T. Watanabe, Y. Sakoda, M. Hatta, Y. Muramoto, D. Tamura, Y. Sakai-Tagawa, T. Noda, S. Sakabe, M. Imai, Y. Hatta, S. Watanabe, C. Li, S. Yamada, K. Fujii, S. Murakami, H. Imai, S. Kakugawa, M. Ito, R. Takano, K. Iwatsuki-Horimoto, M. Shimojima, T. Horimoto, H. Goto, K. Takahashi, A. Makino, H. Ishigaki, M. Nakayama, M. Okamatsu, K. Takahashi, D. Warshauer, P. A. Shult, R. Saito, H. Suzuki, Y. Furuta, M. Yamashita, K. Mitamura, K. Nakano, M. Nakamura, R. Brockman-Schneider, H. Mitamura, M. Yamazaki, N. Sugaya, M. Suresh, M. Ozawa, G. Neumann, J. Gern, H. Kida, K. Ogasawara and Y. Kawaoka, 2009: In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. Nature; doi:10.1038/nature08260.

Iwami, S., Y. Takeuchi and X. Liu, 2007: Avian-human influenza epidemic model. Math. Biosci., 207, 1-25.

Karasin, A. I., M. M. Schutten, L. A. Cooper, C. B. Smith, K. Subbarao, G. A. Anderson, S. Carman and C. W. Olsen, 2000: Genetic characterization of H3N2 influenza viruses isolated from pigs in North America, 1977-1999: evidence for wholly human and reassortant virus genotypes. Virus Res., 68, 71-85.

Kim, K. I., Z. Lin and L. Zhang, 2010: Avian-human influenza epidemic model with diffusion. Nonlinear Anal-Real., 11, 313-322.

Lange, E., D. Kalthoff, U. Blohm, J. P. Teifke, A. Breithaupt, C. Maresch, E. Starick, S. Fereidouni, B. Hoffmann, T. C. Mettenleiter, M. Beer and T. W. Vahlenkamp, 2009: Pathogenesis and transmission of the novel swine-origin influenza virus A/H1N1 after experimental infection of pigs. J. Gen. Virol., 90, 2119-2123.

Le Menach, A., E. Vergu, R. F. Grais, D. L. Smith and A. Flahault, 2006: Key strategies for reducing spread of avian influenza among commercial poultry holdings: lessons for transmission to humans. Proc. R. Soc. Lond. B. Biol. Sci., 273, 2467-2475.

Lee, B. Y., S. T. Brown, P. Cooley, M. A. Potter, W. D. Wheaton, R. E. Voorhees, S. Stebbins, J. J. Grefenstette, S. M. Zimmer, R. K. Zimmerman, T. M. Assi, R. R. Bailey, D. K. Wagener and D. S. Burke, 2009: Simulating School Closure Strategies to Mitigate an Influenza Epidemic. J. Public Health Manag. Pract.

Lekcharoensuk, P., K. M. Lager, R. Vemulapalli, M. Woodruff, A. L. Vincent and J. A. Richt, 2006: Novel swine influenza virus subtype H3N1, United States. Emerg. Infect. Dis., 12, 787–794.

Lindstrom, S., G. Rebecca, B. Amanda, S. Bo, E. Shannon, B. LaShondra, B. Nathelia, S. Katrina, G. Larisa, V. Julie and K. Alexander, 2012: Human Infections with

Novel Reassortant Influenza A(H3N2)v Viruses, United States, 2011. Emerg. Infect. Dis., 18, 834-837.

Longini, I. M., Jr., M. E. Halloran, A. Nizam and Y. Yang, 2004: Containing pandemic influenza with antiviral agents. Am. J. Epidemiol., 159, 623-633.

Longini, I. M., A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D. A. T. Cummings and M. E. Halloran, 2005: Containing Pandemic Influenza at the Source. Science, 309, 1083-1087.

Lynn, J., 2009: Swine flu alert prompts pork import bans Reuters. Geneva.

Ma, W., K. M. Lager, A. L. Vincent, B. H. Janke, M. R. Gramer and J. A. Richt, 2009: The Role of Swine in the Generation of Novel Influenza Viruses. Zoonoses Public Health, 56, 326–337.

Moreno, A., L. Di Trani, L. Alborali, G. Vaccari, I. Barbieri, E. Falcone, E. Sozzi, S. Puzelli, G. Ferri and P. Cordioli, 2010: First Pandemic H1N1 Outbreak from a Pig Farm in Italy. Open Virol. J., 4, 52-56.

Mossong, J., N. Hens, M. Jit, P. Beutels, K. Auranen, R. Mikolajczyk, M. Massari, S. Salmaso, G. S. Tomba, J. Wallinga, J. Heijne, M. Sadkowska-Todys, M. Rosinska and W. J. Edmunds, 2008: Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med., 5, e74-e74.

Myers, K. P., C. W. Olsen and G. C. Gray, 2007: Cases of swine influenza in humans: a review of the literature. Clin. Infect. Dis., 44, 1084-1088.

Myers, K. P., C. W. Olsen, S. F. Setterquist, A. W. Capuano, K. J. Donham, E. L. Thacker, J. A. Merchant and G. C. Gray, 2006: Are swine workers in the United States at increased risk of infection with zoonotic influenza virus? Clin. Infect. Dis., 42, 14-20.

NAADSM Development Team, 2008: NAADSM version number 3.1.24. Free program distributed via the Internet at http://www.naadsm.org.

OIE, 2009: World Animal Health Information Database Weekly Disease Information: A/H1N1 influenza, Canada (Immediate notification : 05/05/2009). Available at http://www.oie.int/wahis_2/public%5C..%5Ctemp%5Creports/en_imm_0000008065_20090505_191855.pdf (accessed 28 April 2010). Paris.

OIE, 2009-2010: World Animal Health Information Database Weekly Disease Information. Available at http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/reportarchive (accessed on 22 April 2010). Paris.

Olsen, C. W., L. Brammer, B. C. Easterday, N. Arden, E. Belay, I. Baker and N. J. Cox, 2002: Serologic evidence of H1 swine Influenza virus infection in swine farm residents and employees. Emerg. Infect. Dis., 8, 814-819.

Olsen, C. W., A. I. Karasin, S. Carman, Y. Li, N. Bastien, D. Ojkic, D. Alves, G. Charbonneau, B. M. Henning, D. E. Low, L. Burton and G. Broukhanski, 2006: Triple reassortant H3N2 influenza A viruses, Canada, 2005. Emerg. Infect. Dis., 12, 1132-1135.

Pasma, T. and T. Joseph, 2010: Pandemic (H1N1) 2009 infection in swine herds, Manitoba, Canada. Emerg. Infect. Dis., 16, 706-708.

Pereda, A., J. Cappuccio, M. A. Quiroga, E. Baumeister, L. Insarralde, M. Ibar, R. Sanguinetti, M. L. Cannilla, D. Franzese, O. E. Escobar Cabrera, M. I. Craig, A. Rimondi, M. Machuca, R. T. Debenedetti, C. Zenobi, L. Barral, R. Balzano, S. Capalbo, A. Risso and C. J. Perfumo, 2010: Pandemic (H1N1) 2009 outbreak on pig farm, Argentina. Emerg. Infect. Dis., 16, 304-307.

Pourbohloul, B., A. Ahued, B. Davoudi, R. Meza, L. A. Meyers, D. M. Skowronski, I. Villaseñor, F. Galván, P. Cravioto, D. J. D. Earn, J. Dushoff, D. Fisman, W. J. Edmunds, N. Hupert, S. V. Scarpino, J. Trujillo, M. Lutzow, J. Morales, A. Contreras, C. Chávez, D. M. Patrick and R. C. Brunham, 2009: Initial human transmission dynamics of the pandemic (H1N1) 2009 virus in North America. Influenza Other Respi. Viruses, 3, 215-222.

Rahmandad, H. and J. Sterman, 2008: Heterogeneity and Network Structure in the Dynamics of Diffusion: Comparing Agent-Based and Differential Equation Models. Manage Sci, 54, 998–1014.

Ramirez, A., A. W. Capuano, D. A. Wellman, K. A. Lesher, S. F. Setterquist and G. C. Gray, 2006: Preventing zoonotic influenza virus infection. Emerg. Infect. Dis., 12, 997.

Reeves, A., M. Talbert, M. D. Salman and A. E. Hill, 2013: Development of a stochastic, individual-based modeling framework for within-herd transmission of highly infectious animal diseases. Prev. Vet. Med., (submitted).

Reuters, 2009: FACTBOX-Flu triggers pig and pork import bans worldwide. Reuters.

Robinson, J. L., B. E. Lee, J. Patel, N. Bastien, K. Grimsrud, R. F. Seal, R. King, F. Marshall and Y. Li, 2007: Swine influenza (H3N2) infection in a child and possible community transmission, Canada. Emerg. Infect. Dis., 13, 1865-1870.

Saenz, R. A., H. W. Hethcote and G. C. Gray, 2006: Confined animal feeding operations as amplifiers of influenza. Vector Borne Zoonotic Dis., 6, 338-346.

Shaban, N., M. Andersson, A. Svensson and T. Britton, 2009: Household epidemics: modelling effects of early stage vaccination. Biom. J., 51, 408-419.

Shope, R. E., 1931: Swine influenza : iii. Filtration experiments and etiology. J. Exp. Med., 54, 373-385.

Smith, G. J. D., D. Vijaykrishna, J. Bahl, S. J. Lycett, M. Worobey, O. G. Pybus, S. K. Ma, C. L. Cheung, J. Raghwani, S. Bhatt, J. S. M. Peiris, Y. Guan and A. Rambaut, 2009: Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. Nature, 459, 1122-1125.

Song, M. S., J. H. Lee, P. N. Pascua, Y. H. Baek, H. I. Kwon, K. J. Park, H. W. Choi, Y. K. Shin, J. Y. Song, C. J. Kim and Y. K. Choi, 2010: Evidence of human-to-swine transmission of the pandemic (H1N1) 2009 influenza virus in South Korea. J. Clin. Microbiol., 48, 3204-3211.

Sreta, D., S. Tantawet, S. N. Na Ayudhya, A. Thontiravong, M. Wongphatcharachai, J. Lapkuntod, N. Bunpapong, R. Tuanudom, S. Suradhat, L. Vimolket, Y. Poovorawan, R. Thanawongnuwech, A. Amonsin and P. Kitikoon, 2010: Pandemic (H1N1) 2009 virus on commercial swine farm, Thailand. Emerg. Infect. Dis., 16, 1587-1590.

Statistics Canada, 2007: Farm Operators by Farm Type and Province (2001 and 2006 Censuses of Agriculture) (Canada) (Summary Tables). Last updated May 16, 2007. Statistics Canada:http://www40.statcan.ca/l01/cst01/agrc22a.htm?sdi=farm%20operators (Accessed on 28 March 2010).

Statistics Canada, 2007(b): Population and Dwelling Counts, for Canada, Provinces and Territories, 2006 and 2001 Censuses, 100% Data (table). “Population and dwelling count highlight tables, 2006 Census.” “2006 Census: Release topics.” Census Statistics Canada Catalogue no. 97-550-XWE2006002. Ottawa, Ontario. March 13. Statistics Canada:http://www12.statcan.gc.ca/census-recensement/2006/rt-td/pd-pl-eng.cfm/ (Accessed on 28 March 2010).

Statistics Canada, 2007(c): Census Agricultural Regions Boundary Files for the 2006 Census of Agriculture: Reference Guide. Statistics Canada Catalogue no. 92-174-GWE. Ottawa, Ontario. May 16. Statistics Canada: http://www.statcan.ca/english/freepub/92-174-GIE/92-174-GIE2007000.htm (Accessed on 28 March 2010).

Statistics Canada, 2007(d): GeoSuite. 2006 Census (Geography Products: Geographic Data Products). Statistics Canada Catalogue no. 92-150-XBB. Ottawa, Ontario. March 13. Statistics Canada:http://www12.statcan.gc.ca/census-recensement/2011/geo/ref/geosuite-eng.cfm (Accessed on 28 March 2010).

Stevenson, M. A., R. L. Sanson, M. W. Stern, B. D. O'Leary, M. Sujau, N. Moles-Benfell and R. S. Morris, 2013: InterSpread Plus: a spatial and stochastic simulation model of disease in animal populations. Prev. Vet. Med., 109, 10-24.

Tiensin, T., M. Nielen, H. Vernooij, T. Songserm, W. Kalpravidh, S. Chotiprasatintara, A. Chaisingh, S. Wongkasemjit, K. Chanachai, W. Thanapongtham, T. Srisuvan and A. Stegeman, 2007: Transmission of the highly pathogenic avian influenza

virus H5N1 within flocks during the 2004 epidemic in Thailand. J. Infect. Dis., 196, 1679-1684.

Torremorell, M., M. Allerson, C. Corzo, A. Diaz and M. Gramer, 2012: Transmission of Influenza A Virus in Pigs. Transbound Emerg Dis, 59, 68-84.

Tuite, A. R., A. L. Greer, M. Whelan, A. L. Winter, B. Lee, P. Yan, J. Wu, S. Moghadas, D. Buckeridge, B. Pourbohloul and D. N. Fisman, 2010: Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza. Can. Med. Assoc. J., 182, 131-136.

van Gemert, C., M. Hellard, E. S. McBryde, J. Fielding, T. Spelman, N. Higgins, R. Lester, H. Vally and I. Bergeri, 2011: Intrahousehold transmission of pandemic (H1N1) 2009 virus, Victoria, Australia. Emerg. Infect. Dis., 17, 1599-1607.

Vincent, A. L., K. M. Lager, K. S. Faaberg, M. Harland, E. L. Zanella, J. R. Ciacci-Zanella, M. E. Kehrli, Jr., B. H. Janke and A. Klimov, 2010: Experimental inoculation of pigs with pandemic H1N1 2009 virus and HI cross-reactivity with contemporary swine influenza virus antisera. Influenza Other Respi. Viruses, 4, 53-60.

Vincent, A. L., K. M. Lager, M. Harland, A. Lorusso, E. Zanella, J. R. Ciacci-Zanella, M. E. Kehrli and A. Klimov, 2009: Absence of 2009 pandemic H1N1 influenza A virus in fresh pork. PLoS One, 4, e8367. doi: 8310.1371/journal.pone.0008367.

Vincent, A. L., W. Ma, K. M. Lager, B. H. Janke and J. A. Richt, 2008: Swine influenza viruses a North American perspective. Adv. Virus Res., 72, 127-154.

Vynnycky, E. and R. White, 2010: An introduction to infectious disease modelling. Oxford University Press, Oxford, UK.

Welsh, M. D., P. M. Baird, M. P. Guelbenzu-Gonzalo, A. Hanna, S. M. Reid, S. Essen, C. Russell, S. Thomas, L. Barrass, F. McNeilly, J. McKillen, D. Todd, V. Harkin, S. McDowell, B. Choudhury, R. M. Irvine, J. Borobia, J. Grant and I. H. Brown, 2010: Initial incursion of pandemic (H1N1) 2009 influenza A virus into European pigs. Vet. Rec., 166, 642-645.

WHO, 2009: Statement to the press by WHO Director-General Dr Margaret Chan WHO.

Wu, J. T., S. Riley, C. Fraser and G. M. Leung, 2006: Reducing the impact of the next influenza pandemic using household-based public health interventions. PLoS Med., 3, e361-e361.

Yang, Y., J. D. Sugimoto, M. E. Halloran, N. E. Basta, D. L. Chao, L. Matrajt, G. Potter, E. Kenah and I. M. Longini, Jr., 2009: The transmissibility and control of Pandemic Influenza A (H1N1) virus. Science, 326, 729-733.

Zhou, N. N., D. A. Senne, J. S. Landgraf, S. L. Swenson, G. Erickson, K. Rossow, L. Liu, K. Yoon, S. Krauss and R. G. Webster, 1999: Genetic reassortment of avian, swine, and human influenza A viruses in American pigs. J. Virol., 73, 8851-8856.

Zimmer, S. M. and D. S. Burke, 2009: Historical Perspective — Emergence of Influenza A (H1N1) Viruses. N. Engl. J. Med., 361, 279-285.

Table 3.1: Description of study populations and probability density functions of the size of units used for the simulation of influenza spread between swine and human populations in a country of Ontario, Canada.

Population units	Total no. of units	Distribution of size of units	Total no. of individuals
Swine-herds (SH)	488	Uniform(min = 500; max = 2500)	733,107
Swine-worker-households (SWH)	733	Truncated Poisson(mean = 3, min = 2; max = 7)	2,325
Rural non-swine-worker-households (RH)	7,879	Truncated Poisson(mean = 3, min=2; max=7)	25,521
Urban-households(UH)	21,095	Truncated Poisson(mean = 3, min = 2; max = 6)	54,038
Total	30,195		814,991

Units refers to swine herds or households and individual means a pig or a person.

Table 3.2: Parameters and their probability density functions for swine farms used in the simulation of influenza spread between swine and human populations in a county of Ontario, Canada.

Input parameters	Individual	Herd level	References
Latent period (day)	1[a]	Fixed value of 1[b]	(Lange et al., 2009, Brookes et al., 2010, Vincent et al., 2010)[a];
Subclinical infectious (day)	0–6[a]	BetaPERT(0, 3, 6)[b]	Generated from the individual-level parameters using WH 0.9.5 software[† b];
Clinical infectious (day)	1–15[a]	BetaPERT (5; 25;45)[b]	(Blaskovic et al., 1970, Desrosiers et al., 2004)[c];
Immune period (day)	365–840[c]	Fixed value 366[d]	Assumed permanent immunity by using a value greater than the duration of the simulation period (365 days)[d]

[†]WH 0.9.5 is the software that simulate within-herd disease transmission stochastically and generates herd-level durations of disease states (Reeves et al., 2013).
Parameters were extracted from the references with the matching superscript letters.

Table 3.3: Parameters and their probability density functions for households used in the simulation of influenza spread between swine and human populations in a county of Ontario, Canada.

Input parameters	Individual	Household	References
Latent period (day)	1–3[a]	BetaPERT (1, 2, 3)[b]	(Boëlle et al., 2009, Pourbohloul et al., 2009, Tuite et al., 2010)[a];
Subclinical infectious (day)	0–3[a]	BetaPERT (0, 2,3)[b]	Generated from the individual-level parameters using WH 0.9.5 software[† b];
Clinical infectious (day)	4–10[a]	BetaPERT (4, 12, 20)[b]	Assumed permanent immunity by using a value greater than the duration of the simulation period (365 days)[c]
Immune period (day)	-	Fixed value of 366[c]	

[†]WH 0.9.5 is the software that simulate within-herd disease transmission stochastically and generates herd-level durations of disease states (Reeves et al., 2013).
Parameters were extracted from the references with the matching superscript letters.

Table 3.4: Contact structure and influenza transmission parameters used in the simulation of influenza spread between swine and human populations in a county of Ontario, Canada.

Contact type	Mean contacts/day	Distance distribution of recipient units (km)	Probability of infection (Low/ medium/high)	References
Swine to swine				
SH-SH (Direct contact)	0.06[a]	BetaPERT(0.8, 20, 100)[b]	1[c]	(Bates et al., 2001, Christensen et al., 2008) and unpublished data from Ontario Veterinary College[a]; Assumption based on the informed judgement of the co-authors[b]; Assumed based on experimental studies (Lange et al., 2009, Brookes et al., 2010, Vincent et al., 2010)[c]; Bases on the assumptions explained in the main text[d]; Assumed once/week based on the informed judgement of the co-authors and multiplied by half the individual contact rate from Lee et al., (2009) and Mossong et al., 2008 (2008)[e]; Derived from R0 value of pH1N1 2009 as explained the text[f]. Assumed 5 times/week based on the informed judgment of co-authors multiplied by half the individual contact rate from Lee et al., (2009) and Mossong et al., 2008 (2008)[g]; Assumed once/year based on the informed judgment of the co-authors and multiplied by the individual contact rate from Lee et al., (2009) and Mossong et al., 2008 (2008)[h]; Assumed twice/year based on the informed judgment of co-authors multiplied by the individual contact rate from Lee et al., (2009) and Mossong et al., 2008 (2008)[i]; Based on the individual contact rate from Lee et al., (2009) and Mossong et al., 2008 (2008)[j]
SH-SH (Indirect contact)	0.196[a]	BetaPERT (0.8, 20,100)[b]	0.01[b]	
Swine to human				
SH-SWH	1[d]	Uniform(0.1, 0.5)[b]	(0.024/0.3/ 1[d]	
Human to swine				
SWH–SH	1[d]	Uniform(0.1, 0.5)[c]	(0.024/ 0.3/1)[d]	
Human to human				
SWH-SWH	0.857[e]	BetaPERT(0.5, 20, 100)[b]	(0.024)[f]	
SWH-RH	4.286[g]	BetaPERT(0.1, 10, 30)[b]	(0.024)[f]	
SWH-UH	0.857[e]	BetaPERT(1, 30, 65)[b]	(0.024)[f]	
RH-SWH	0.857[e]	BetaPERT(0.1, 10, 30)[b]	(0.024)[f]	
RH-RH	4.286[g]	BetaPERT(0.01, 20, 100)[b]	(0.024)[f]	
RH-UH	0.857[e]	BetaPERT(1, 30, 65)[b]	(0.024)[f]	
UH-SWH	0.036[h]	BetaPERT(1, 30, 65)[b]	(0.024)[f]	
UH-RH	0.071[i]	BetaPERT(1, 30, 65)[b]	(0.024)[f]	
UH-UH	12.893[j]	BetaPERT(0.01, 10, 30)[b]	(0.024)[f]	

Parameters were extracted from the references with the matching superscript letters.

Key: SH = Swine herds, SWH = Swine-worker-households, RH = Rural non-swine-worker-households, UH = Urban households.

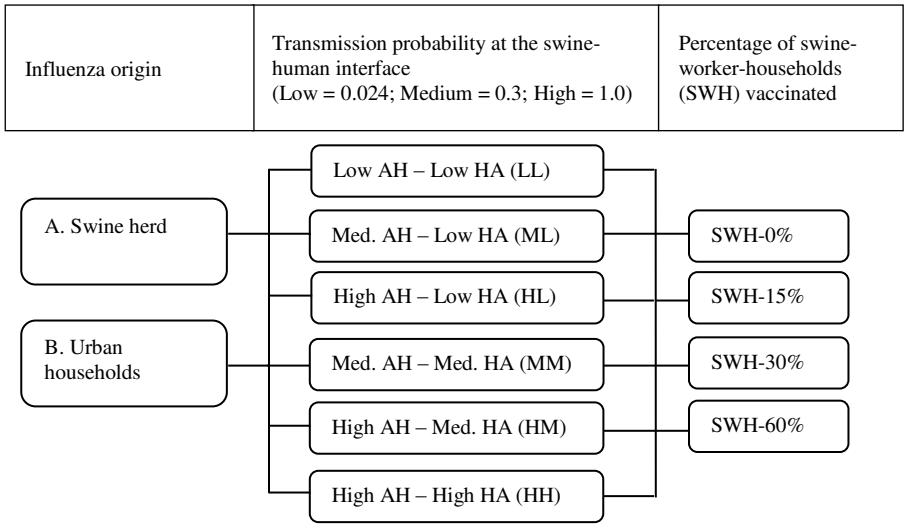

Figure 3.1: Graphical description of scenarios used for the simulation of the simultaneous spread of pandemic influenza H1N1 2009 virus between swine and human populations in a county of Ontario, Canada. Key: AH = animal to human, HA = human to animal, SWH- 0% to 60% refers to the percentage of swine worker households vaccinated prior to the disease outbreak with the assumption of a 100% protective effect.

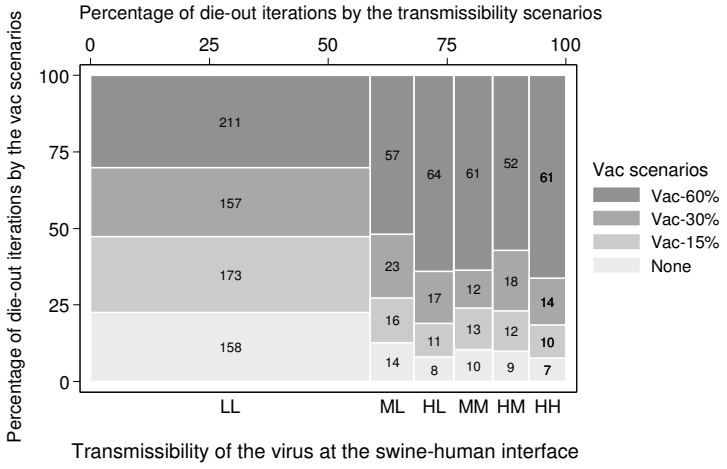

Figure 3.2: Percentage of iterations with stochastic 'die-outs' (<1% of units infected) of 24 scenarios of the simultaneous spread of the influenza (swine origin) between swine and human populations. These scenarios consisted of combinations of the six levels of transmissibility of the virus at the swine-human interface and four levels of the vaccination coverage of swine-worker-household population. Each scenario was simulated for 1,000 iterations. Transmissibility abbreviations are outlined in Figure 3.1.

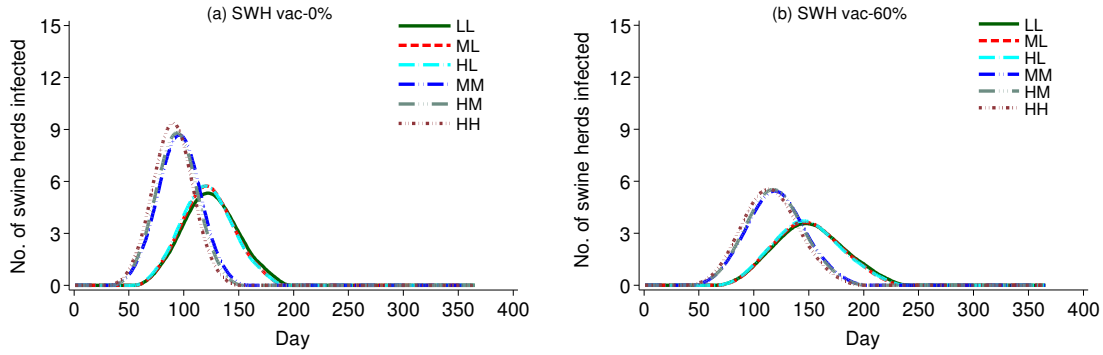

Figure 3.3: Epidemic curves illustrating the spread of the influenza in the swine herds (SH) in the case of virus originating in the urban households under the different levels of transmissibility of the virus at the interface, and at the two levels of the vaccination coverage of the swine-worker-households (SWH). As the effects of transmissibility at the 15% to 30% vaccination coverage levels were similar to the scenario when none was vaccinated, only the epidemic curves at 0% and 60% vaccination coverage levels are shown. Transmissibility abbreviations are outlined in Figure 3.1.

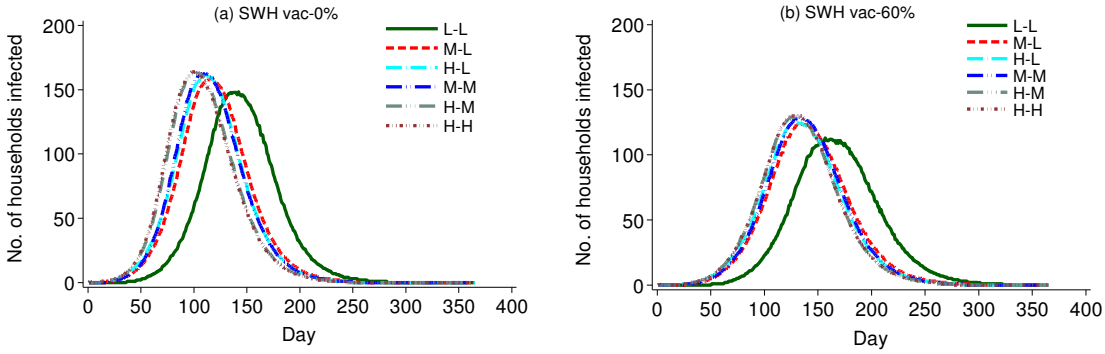

Figure 3.4: Epidemic curves illustrating the spread of the influenza in the household population in the case of virus originating in a swine herd under the different levels of transmissibility of the virus at the interface, and at two levels of the vaccination coverage of the swine-worker-households (SWH). As the effects of the transmissibility of the virus of the 15% to 30% vaccination coverage were similar to that of a scenario when none was vaccinated, only the epidemic curves at 0% and 60% vaccination coverage are shown. Transmissibility abbreviations are outlined in Figure 3.1.

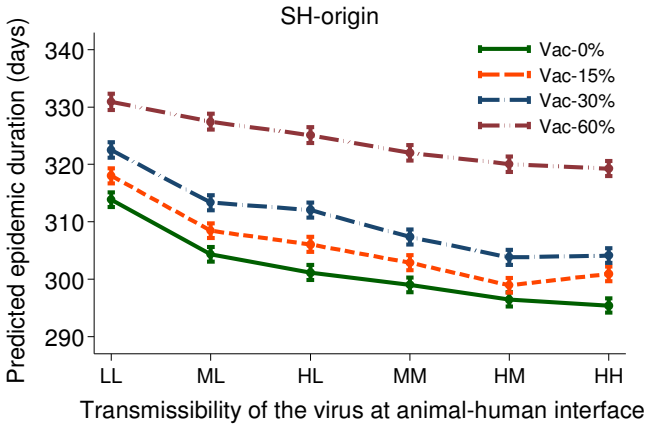

Figure 3.5: The interaction plot for the transmissibility of the virus at the interface and the vaccination of the swine-worker household population on the predicted median epidemic duration for the influenza outbreaks in the case of the virus originating in a swine herd. The effects were similar in the case of virus originating in the urban households. Key: SH = swine herds; SWH = swine-worker households; RH = rural non-swine-worker households, UH = urban households. Transmissibility abbreviations are outlined in Figure 3.1.

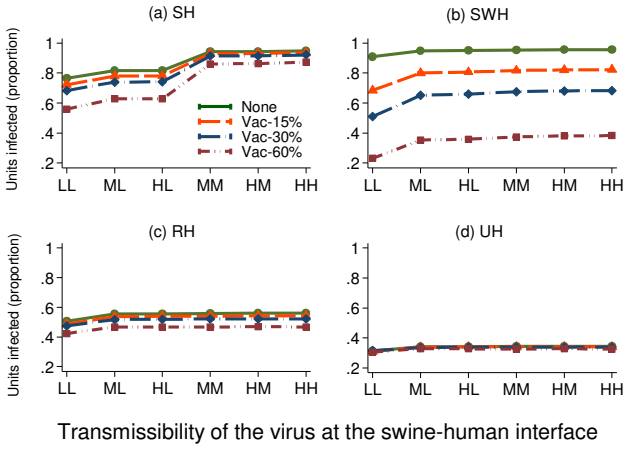

Figure 3.6: The interaction plots for the transmissibility of the virus at the interface and the vaccination of the SWH population on the proportion of units infected for the influenza outbreaks in the case of the virus originating in swine herd. The effects were similar in the case of virus originating in the urban households. Key: SH = swine herds; SWH = swine-worker households; RH = rural non-swine-worker households, UH = urban households. Transmissibility abbreviations are outlined in Figure 3.1.

Chapter 4

One-Health Simulation Modeling: Assessment of Control Strategies against the Spread of Influenza between Swine and Human Populations using NAADSM*

* Dorjee, S., C. W. Revie, Z. Poljak, W. B. McNab, J. T. McClure and J. Sanchez, 2013: One-Health simulation modeling: Assessment of control strategies against the spread of influenza between swine and human populations using the NAADSM. Transboundary and Emerging Diseases (Submitted)

4.1 Abstract

Simulation models implemented using a range of parameters offer a useful approach to identifying effective disease intervention strategies. The objective of this study was to evaluate the effects of key control strategies to mitigate the simultaneous spread of influenza among and between swine and human populations. We used the pandemic H1N1 2009 virus as a case study. The study population included swine herds (488 herds) and households-of-people (29,707 households) within a county in Ontario, Canada. Households were categorized as: (i) rural households with swine workers, (ii) rural households without swine workers, and (iii) urban households without swine workers. Seventy two scenarios were investigated based on a combination of the control parameters: speed of detection, quarantine strategy, effectiveness of movement restriction, and ring vaccination strategy, all assessed at three levels of transmissibility of the virus at the swine-human interface. Results showed that the speed of detection of the infected units combined with the quarantine strategy had the largest impact on the size and duration of outbreaks. A combination of fast to moderate speed of the detection (where infected units were detected within five to 10 days since first infection) and quarantine of the detected units alone contained the outbreak within the swine population in most of the simulated outbreaks. Ring vaccination had no added beneficial effect. In conclusion our study suggests that the early detection (and therefore effective surveillance) and effective quarantine had the largest impact in the control of the influenza spread, consistent with earlier studies. To our knowledge no study had

previously assessed the impact of the combination of different intervention strategies involving the simultaneous spread of influenza between swine and human populations.

Keywords: One-health, modeling, zoonotic diseases, influenza, pigs, humans, NAADSM

4.2 Introduction

Pandemics caused by influenza A viruses, including the most recent outbreak involving the pandemic influenza A/H1N1 2009 virus (pH1N1), continue to present a significant zoonotic threat to human and animal populations. Constant outbreaks of H5N1 in Asia (OIE, 2013), and recent outbreaks of a novel swine-origin H3N2 variant virus in the United States (Lindstrom et al., 2012), and bird-origin H7N9 virus in China (Gao et al., 2013, Uyeki and Cox, 2013) are examples of the current public health concerns. Many countries have developed influenza pandemic preparedness plans following the World Health Organization guidelines to prevent or mitigate the impact of future influenza pandemics (WHO, 2011). The main mitigation measures against influenza pandemics are public health measures (also known as non-pharmaceutical) and medical or pharmaceutical interventions (WHO, 2005, Ferguson et al., 2006, Halloran et al., 2008, Lee et al., 2009). Public health measures include personal hygiene such as hand washing, the use of personal protective equipment (face-masks, gloves, etc.), and social distancing measures (quarantine and isolation, school closure, restrictions on gathering at public events and on travel, etc.). The main medical interventions against influenza include anti-viral prophylaxis and treatment, as well as vaccination.

Recently, computer simulation and mathematical models have been widely used to evaluate the effectiveness of intervention strategies against influenza pandemics. In human populations these have included simulations that evaluate individual intervention strategies or a combination of such interventions (Lee et al., 2009, Dorjee et al., 2012). Relatively few simulation modeling studies have been reported that seek to assess the control of influenza outbreaks in animals (Dorjee et al., 2012). Only, one modeling study has investigated the simultaneous spread of influenza among and between swine and human populations (Saenz et al., 2006). This is despite the fact that swine are widely considered to be a potential host for the emergence of novel pandemic influenza strains, and frequent reports of the transmission of influenza between swine and people (Myers et al., 2006, Myers et al., 2007, Ma et al., 2009, Zimmer and Burke, 2009, Lindstrom et al., 2012). Several countries have reported the transmission of pH1N1 2009 virus from humans to swine (Nelson et al., 2012). Therefore, it is imperative to understand the transmission dynamic of influenza and the effectiveness of the mitigation strategies at the swine-human interface.

Models enable the researcher to simulate thousands of virtual influenza outbreaks and evaluate the effectiveness of control strategies under a range of scenarios, which cannot feasibly be implemented in real-world situations. The outcomes of such studies can guide and inform the development of contingency plans and policy for preparedness and response to future pandemic threats (Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Halloran et al., 2008, Basta et al., 2009,

Gojovic et al., 2009, Tuite et al., 2010). A systematic review of models evaluating effectiveness of combination strategies for pandemic influenza response in human populations concluded that the combination of several control measures proved more beneficial than the use of only one particular measure (Lee et al., 2009). Most models in human populations assessed the intervention strategies that were targeted at the individual. Few studies in humans have also investigated the spread and control of influenza at the household level (Ferguson et al., 2005, Longini et al., 2005, Wu et al., 2006, Fraser, 2007, Shaban et al., 2009). Indeed, these studies noted that targeting intervention strategies such as isolation and quarantine, or vaccination and anti-viral prophylaxis at the household level was more pragmatic and likely more effective than at the individual level. In this case, the approach is similar to the types of disease control strategy that are implemented for livestock at the farm level. Targeting intervention measures at the household level in human population offers the added advantage of ensuring that the granularity of the simulation unit is the same for both animal and human populations. This enables the modeling of zoonotic disease spread and control between animal and human population simultaneously using readily available modeling platform like North American Animal Disease Spread Model (NAADSM). The NAADSM has built-in features to evaluate the effectiveness of the main disease control strategies against contagious diseases of livestock. These include the speed of disease detection and reporting, forward contact tracing of infected units, quarantine, vaccination and

depopulation with or without zoning (disease control area within a specified radius) (Harvey et al., 2007).

While the previous study (Chapter 3) assessed the transmission dynamic of the pH1N1 2009 at the swine-human interface, this study was aimed to further use NAADSM to evaluate different control strategies against the spread of contagious zoonotic pathogens among and between swine and human populations. Specifically it evaluated the effectiveness of different intervention strategies such as the speed of detection of outbreaks, quarantine and movement control, and ring vaccination against the simultaneous spread of pH1N1 2009 between swine and human populations.

4.3 Materials and Methods

4.3.1 Study area and populations

The same study area and populations described in Chapter 3 were used for this study. Briefly a county within the province of Ontario, Canada, with relatively high density of swine farms along with the existence of a range of rural and urban areas (one city and four towns) was selected. Swine herds (SH) and household population data were extracted from the official census of 2006 (Statistics Canada, 2007, Statistics Canada, 2007(b)) to ensure the correct representation of each of these populations within the model. Household populations were categorized as: (i) rural households with at least one swine worker (SWH), (ii) rural households without swine workers (RH), and (iii) urban households without swine workers (UH). The SWH units served as the bridging population for pH1N1 2009 virus transmission between swine and human populations.

The sizes of swine herds and households were generated as described in Chapter 3. The study population consisted of: 488 SH, 733 SWH, 7,879 RH and 21,095 UH. Since the specific geographic coordinates of all units were not available in the official census data, their geo-coordinate locations were randomly assigned within the agricultural areas (SH, SWH, and RH) and urban areas of the county.

4.3.2 Model structure

4.3.2.1 North American Animal Disease Spread Model (NAADSM)

The supercomputer version of NAADSM 3.1.24 (NAADSM Development Team, 2008) was used for the construction and simulation of the models. NAADSM is a computer modeling platform for simulating the spread and control of contagious diseases in animal populations, either of the same or different species, or production types. It uses a stochastic, spatially explicit, state-transition method. The unit of disease spread is simulated at the farm or household level. It has provisions to evaluate the effectiveness of a number of different intervention strategies, such as: speed of detection, quarantine and movement control, vaccination, and depopulation. The effectiveness of these measures can be evaluated with or without a disease control zone of a certain radius, along with forward contact tracing. A detailed description of NAADSM has been provided by Harvey et al, (2007) as well as by Hill and Reeves (2006).

4.3.2.2 Disease states and transmission

The disease spread model structure (susceptible-exposed-infectious-recovered (SEIR)) and, contact structure among swine herds (SH to SH), between SH and SWH, and

among SWH, RH and UH were described in Chapter 3. Susceptible units consisted of herds or households that were not infected but were vulnerable to an infection; exposed/latent units were those that had been infected but were not shedding organisms; infectious units are units shedding organisms; while recovered units were those that had recovered and were immune to further infection. Permanent immunity was simulated by setting duration of immunity longer than the simulated period (365 days).

For the influenza spread between SH and SWH, a contact was assumed to have occurred when the swine workers came in contact with pigs on farms (SH) during the course of their daily work. Similarly, for its spread amongst households, a contact was assumed to have occurred implicitly when an individual from an infectious household established an adequate contact with individuals from other households at any place, such as schools, workplaces or other social congregations. Individuals who become newly infected through contact with infectious person outside their home in turn infect other members at home and outside their home. The influenza transmissions between infectious and susceptible units through direct and indirect (spread between SH units through contaminated fomites) contacts were simulated as a function of contact rate, the probability of infection per contact and movement distance distribution between the units.

Furthermore, all assumptions of the model, including influenza transmission between units in different disease states, their transition from one state to another, and parameters

relating to disease states, contact frequencies between pairs of units, and their transmission probabilities outlined in Chapter 3 were adopted for this study.

4.3.2.3 Control strategies

The scenarios used for the evaluation of the control strategies against the influenza spread between swine and human populations are outlined in Figure 4.1. Three control strategies were evaluated: (i) quarantine without zoning where only detected units were quarantined (No-zone strategy), (ii) quarantine with zoning where all units (both swine herd and household populations) within a zone of 3 km radius were quarantined (With-zone strategy), and (iii) With-zone strategy plus ring vaccination of susceptible units (both swine herd and household populations) within a zone of 5 km radius of the detected unit. The size and duration of an influenza outbreak will depend on how soon an outbreak is detected to implement control measures, the type of control strategies, and effectiveness of implementation of these control strategies. Therefore, the effectiveness of these control strategies were evaluated at three levels of speed of detection (slow, moderate and fast), two levels of the effectiveness of movement control of the quarantined units (less-effective and effective), and two levels of the speed of commencement of ring vaccination (slow-trigger and fast-trigger). Furthermore, these control strategies were evaluated at three levels of transmissibility of the virus at the swine-human interface: (i) low animal to human - low human to animal (LL), (ii) medium animal to human - low human to animal (ML), and (iii) high animal to human - medium human to animal (HM). Seventy two scenarios of various combinations of the

control strategies and the transmissibility of the virus at the swine-human interface were simulated.

Detection in NAADSM is defined as the product of two probabilities, (a) the probability of observing clinically ill and infectious units over time multiplied by (b) the probability of reporting such an observed unit over time (Hill and Reeves, 2006, Harvey et al., 2007). Each of these probabilities changes over time and it can be incorporated into the model as a linear function (Table 4.1 (a)). The probability of observing clinical signs would be expected to increase over time as more pigs in a swine herd or individuals in a household exhibit clinical signs. Similarly the probability of reporting the detected infected units would be expected to increase over time due to a greater awareness following detection of the first few infected units. The fast, moderate and slow detections were defined as detection of 98% of infected units in 5, 10 and 20 days, respectively (Table 4.1 (a)). Not all infected units would be detected and reported. In this model, we assumed 2% of the infected units would never be detected. Furthermore, the detection was assumed to be 100% specific.

In NAADSM once infected units were detected, they were quarantined and no direct contact from or to these units was allowed. However, indirect contacts from and to the detected units was allowed. In the models the influenza spread was simulated through both direct and indirect contacts among SH units, direct contact from SWH to SH units, and indirect contact from SH to SWH, and among household populations (SWH, RH and UH). To accommodate this in NAADSM an area of five-meter radius zone was

imposed around a given detected unit (SHs and households) to restrict even the indirect contact to achieve the No-zone quarantine strategy. For the quarantine with zone strategy both direct and indirect contacts of all susceptible units within the 3 km radius of a detected unit were restricted. Forward contact tracing of all the direct and indirect contacts upon the detection of an infected unit was implemented for all population types. However, backward tracing was not implemented as the NAADSM version used for this study does not support this feature. All the direct and indirect contacts from the detected unit within 5 days (approximate maximum incubation period of the influenza infection) with a certain percentage of success were conducted (Table 4.1 (a)). All units successfully traced in this manner were automatically quarantined.

Quarantine measures were implemented as a percentage reduction in the baseline contact rate (both direct and indirect contacts) associated with the detected infected units, or of all units within the disease control zone (with-zone strategy). It is not expected that a 100% movement restriction will be achieved in any disease outbreak situation. Therefore two scenarios, (a) less-effective and (b) effective reflecting the effectiveness of movement restrictions of the quarantined units were evaluated (Table 4.1 (a)). Both the movement restriction strategies achieved 95% and 80% reduction of the baseline direct and indirect contact rates. However, in the effective strategy it was achieved in less than 5 days, whereas the same reduction was achieved in less than 10 days in the less-effective strategy. These assumptions were made based on the expert opinion of co-authors as there was no information on these parameters in the literature.

For the control strategy incorporating ring vaccination, the speed of initiation of the vaccination was evaluated using a slow and fast response (Figure 4.1). In the slow-trigger scenario, the vaccination of all susceptible units within a radius of 5 km was triggered upon detecting 25 or more infected units. The fast-trigger began upon detecting 5 or more infected units (Table 4.1 (b)). A seven day delay in the onset of the immunity from the time of vaccination was assumed for households (Bresson et al., 2006, Leroux-Roels et al., 2007, Milne et al., 2009) and SH (Lange et al., 2009). Furthermore, the vaccine was assumed to be 100% protective with permanent immunity. The daily ring vaccination capacity increased from 20 units to a maximum of 300 units per day within five days of starting vaccination for all populations.

For each simulated outbreak, the infection was seeded (index case) into a single randomly selected swine herd (latent state). Each scenario was run for 1,000 iterations. Each of the iterations ran until no infected units remained in the populations or until 365 days had been simulated in the case of persistence of the infection. In all scenarios the randomly selected index swine herd was kept fixed. This was a choice limited by the version of NAADSM 3.1.24 (NAADSM Development Team, 2008) used in this study since it had no feature of seeding the infection randomly in a population at each iteration.

4.3.3 Statistical analyses

The models' outcomes were assessed in terms of the duration of the outbreak and total number of infected units. Summary statistics of these outcomes under each scenario of

speed of detection, quarantine, movement restriction and ring vaccination strategies were generated. Furthermore, the effects of these control strategies at the three levels of the transmissibility of the virus at the interface were evaluated by fitting the survival and negative binomial regression models, for outbreak duration and number of infected units, respectively. Fitting these multivariable models allowed for assessment of interaction effects among control strategies on the outcomes.

An accelerated failure-time (AFT) survival model (using the generalized linear model function) was fitted with outbreak duration as the outcome variable, and the input parameters as the predictor variables. The predictors were entered into the model as categorical variables. The speed of detection was coded as 1 = Slow, 2 = Moderate, and 3 = Fast, quarantine strategy was coded as 1 = No-zone and 2 = With-zone, movement restriction as 1 = Less-effective and 2 = Effective, ring vaccination strategy as 1 = No-vaccination, 2 = Slow-trigger and 3 = Fast-trigger. All meaningful 2-way interactions among the predictors were evaluated and retained in the model if they were significant at $P < 0.05$ and if the difference in the predicted duration of the outbreak between any levels of the interaction term was greater than one-week duration. This criterion was used because even a small difference between the two interaction terms could be statistically significant simply due to large sample size. Akaike Information Criterion (AIC) and Cox-Snell residual plots were used to select the best fitting AFT parametric model and to evaluate the overall fit of the model, as described in Dohoo et al., (2009).

Residuals were evaluated using deviance residual and plotting it against the fitted values or individual predictors.

The effect of the predictors on the size of the outbreak was assessed using a negative binomial regression model. All predictors were entered into the model as described in the survival model above. Instead of building a separate model for each population type, the size of outbreak in each population type was combined into a common outcome variable, and the population type was entered into the model as a categorical predictor (coded as 1 = SH, 2 = SWH, 3 = RH, and 4 = UH). All meaningful two-way interactions among the predictors were examined and retained if they were significant at $P< 0.05$ and if the difference in the predicted number of infected units between any levels of the interaction term was >10 units. Model diagnostics and residuals were evaluated based on the deviance residual.

The results of the survival and the negative binomial regression models were presented in terms of predicted margins of median epidemic duration and number of infected units at the specific representative values of the covariates. All analyses were implemented in Stata version 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

4.4 Results

4.4.1 Epidemic duration

The summary statistics on the effect of the each control strategy (unconditional association) on the duration and size of the outbreak are presented in Table 4.2. The overall median (5^{th}–95^{th} percentiles) of the outbreak duration was 40 (21–234) days. The speed of the detection had a major impact on the outbreak duration. The median duration was approximately two times longer for the slow detection compared with the other two detection levels, and with minimal difference between moderate and fast detection strategies. The median values of the duration of two the quarantine strategies were similar. However, their 95% percentile was relatively longer for the no-zone quarantine strategy (only detected units were quarantined). A similar pattern was observed for the ring vaccination scenarios, with the duration of outbreak longest for the no-vaccination scenario.

The AFT survival model with log-logistic distribution fitted the data best. All the control strategies had statistically significant effects on the outbreak duration. However, the difference in the median duration of outbreaks between ring vaccination and without ring vaccination strategies (ring vaccination category 2 or 3, versus 1) was 5 days, which was practically not meaningful. As such, the ring vaccination strategy variable was excluded from the final model. Significant interactions between the effects of speed of detection and quarantine strategy, and between speed of detection and movement restriction strategy on the outbreak duration were observed. These effects were similar

at all the three levels of the transmissibility of the virus at the interface. Therefore, only the results at the high transmissibility (HM) are presented. The interaction plot of speed of detection and quarantine strategy showed that the effect of these two control strategies depended upon each other (Figure 4.2 (a)). The outbreak duration was 208 days (4 times) longer in the case of no-zone quarantine strategy than with-zone strategy at the slow speed of the detection. However, this difference was small (<4 days) between the two quarantine strategies either at the moderate or fast speed of detection. These effects showed the similar pattern but of lesser magnitude when the movement restriction was more effective than when it was less effective (a difference of 35 days). The interaction plot at the less effective movement restriction strategy only is presented in Figure 4.2 (a). Similarly, the outbreak duration was 238–239 days (6–8 times) longer when the speed of detection was slow than when it was moderate to fast at the no-zone quarantine strategy. However, this difference was relatively smaller (34–40 days longer) under the with-zone quarantine strategy. Similar interaction effects between the speed of detection and the movement restriction strategies on the duration of outbreak were observed (Figure 4.2 (b)) at both levels of the quarantine strategies. However, the magnitude of the difference was much smaller in the no-zone strategy than with-zone strategy.

4.4.2 Epidemic size

The overall percentages of units infected was <1% (median values) for all the population types. The overall 95th percentile of units infected was: SH 10%, SWH 11%,

RH 3% and UH 1%. The summary statistics of the effect of each control strategy (unconditional association) on the size of the outbreak in SH and household populations are presented in Table 4.2. The size of the outbreak (median value) was relatively larger when the detection was slow than moderate or fast, with minimal difference between the latter two detection levels. Although, the median values of the size of outbreak were same between quarantine or movement restriction strategies, or among ring vaccination strategies, the 95% percentiles were considerably larger in the no-zone quarantine than with-zone strategy, and without the ring vaccination than with ring vaccination strategies.

The multivariable negative binomial regression results showed that all the control strategies, except the vaccination strategy (P = 0.172) had a statistically significant effect on the size of the outbreak in all the population types. All two-way interactions between the control strategies and population type on the size of outbreak were significant. Furthermore, the interactions between the speed of detection and quarantine strategy or movement restriction strategy were significant. These effects were again similar at all three levels of the transmissibility of the virus at the interface. Therefore, only results at the high transmissibility of the virus (HM) are presented. The interaction effect between the speed of detection and quarantine strategy on the size of outbreak suggested that imposing quarantine zone around the detected units was beneficial only at the slow detection level (Figure 4.3). No difference in the size of the outbreak was observed between the two quarantine strategies at the moderate or fast detection levels.

These effects were similar in all the population types at both the levels of movement restriction strategies. However, the magnitude of difference between the two quarantine strategies on the size of the outbreak at slow detection was smaller at the effective than less effective movement strategies; less by 33 and 174 units in SH and UH populations, respectively.

Similarly, the size of outbreak between the two movement restriction strategies was significantly different at the slow detection level, with no difference observed in moderate or high detection levels (Figure 4.4). Furthermore, the difference in the effect was observed only at the no-zone quarantine strategy. No difference between the two movement restriction strategies was observed at all levels of the detection at the with-zone quarantine strategy (Figure not shown).

4.4.3 Model and residual diagnostics

The smallest and largest deviance residuals of the AFT survival model were -3.43 and 5.10 respectively. However, less than 1% of the iteration had the deviance residuals above or below ±3. The deviance chi-squared goodness-of-fit test of the negative binomial model did not indicate any lack of fit (P = 0.999). The smallest and largest deviance residuals of negative binomial regression were -4.14 and 9.62 respectively. However, less than 1% of the iterations had the deviance residuals above or below ±3. Therefore the numbers of outlying residuals were as within the acceptable range. Excluding these iterations with outlying residuals had negligible impact on the estimates of both the models. No patterns in the distribution of these outlying residuals were

observed in terms of the covariate patterns. Therefore these residuals might explain the extent of the stochastic variation over and above those explained by the predictors in the models.

4.5 Discussion

This study evaluated the effectiveness of key control strategies against the simultaneous spread of the influenza between swine and human populations using the NAADSM modeling platform. We used pH1N1 2009 virus as a case study because it is easily transmissible between human and swine populations (Howden et al., 2009, Nelson et al., 2012). Simulations of thousands of virtual disease outbreak events under a defined set of input parameters in the model offer a useful tool to identify effective intervention strategies. Results from such studies can provide guidance for making policy decisions and developing disease contingency plans and preparedness for future pandemic threats. To our knowledge (Dorjee et al., 2012) no study has investigated the combination of intervention strategies in situations involving influenza spread between swine and human populations simultaneously.

The results of this study showed that under the assumptions given in the models, differences in speed of detection had the largest effect on the size and duration of the outbreaks. They suggested that a fast to moderate speed of detection (98% detection within 5 to 10 day period) combined with quarantine of detected units along (No-zone quarantine strategy) would control the outbreak in 30–40 days with only a single SH unit and no household unit infected in most instances (Figure 4.2 (a) and Figure 4.3). If

the detection of the majority of infected units (41–98% of the units) was delayed by 11–20 days (Table 4.1), the implementation of the zone-based quarantine strategy (in which both the infected and susceptible units within a 3 km radius of the detected infected units are quarantined) was a better alternative strategy. It could be argued that even the slow detection defined in this study was relatively effective because in reality it might take weeks to a few months to recognize a novel influenza virus originating in swine to be of potential pandemic threat. Its effective transmission from person to person would have to be known before serious public health intervention measures are initiated. However, if control measures were implemented in a manner defined in this study for any serious influenza outbreak in swine, irrespective of knowing its potential pandemic threat to people, the outbreak can be contained within the swine population alone. This would mitigate the likelihood of occurrence of future influenza pandemics. The transmission of the influenza from swine to swine workers can be prevented following strict personal hygiene and protective equipment, including anti-viral prophylaxis in the case of influenza outbreaks, preventing serious threat to human health.

A similar time-frame for speed of detection and implementation of control measures was used for pandemic influenza spread in humans by Longini et al (2005), where delay times of 7, 14, or 21 days after the detection of the first case were evacuated. However, Ferguson et al (2005) used the threshold of 20 or more cases (individuals rather than households) to initiate the implementation of the control strategies, as opposed to a delay measured in days. The finding that speed of detection has the largest impact on the

modeled outcomes in this study was consistent with these other studies that evaluated the similar control strategies targeted at the household level and used zones of a certain radius around infected cases (Ferguson et al., 2005, Longini et al., 2005, Shaban et al., 2009).

The results also suggested that ring vaccination did not offer additional beneficial effect when combined with the detection and the movement restriction level defined in this study. It will likely be challenging to achieve the vaccination capacity of 300 units per day, or early onset of vaccination immunity, and 100% protective level that were assumed in this study. However, even considering this best case scenario, it had no added beneficial effect. Therefore decreasing the ring vaccination capacity or protective level, or delaying onset of the ring vaccination capacity will not make any differences, given the other assumptions in the models. Additional sensitivity analysis to assess the effects of further delaying the speed of detection, reducing effectiveness of movement restriction (that is the compliance rate of quarantine measure) and various ring vaccination options at a wide range of reproductive numbers or varying rates of transmissibility of the virus could be explored in future studies using the present model. For this study we have evaluated the effect of control strategies under the scenario of the pH1N1 seeded (index case) in a swine farm only, due to time constraint and due to the fact that a novel influenza virus may most likely originate in animal than human populations. However, it would be worthwhile for future studies to evaluate the effects

of similar control strategies under scenario where the virus was seeded in a human population.

In this study the control strategies were targeted at the farm or household levels, in contrast to most studies in human populations where control strategies are targeted at the individual (Germann et al., 2006, Nuno et al., 2007, Yasuda and Suzuki, 2009, Tsai et al., 2010, Tuite et al., 2010). However, other studies have highlighted the importance of evaluating the spread and control strategies targeted at the household level together with zones of certain radius (Ferguson et al., 2005, Longini et al., 2005, Wu et al., 2006, Fraser, 2007). These studies justify such approaches on the basis that most influenza transmission occurs within households and that cases tend to be clustered within localities. Furthermore, they highlight the fact that anti-viral treatment and prophylaxes, as well as quarantine measures, are more practical and effective if targeted at the whole household and/or a zone of a certain radius, rather than at the individual. For these reasons the need to estimate influenza spread parameters, such as the reproduction number at household level, had been emphasized (Cauchemez et al., 2004, Ferguson et al., 2005, Fraser, 2007). Therefore, a choice as to the granularity of simulation unit and approach to control strategy evaluation adopted in this study, were consistent with the approaches highlighted as being important by a number of other authors.

The results of this study suggest that NAADSM is a feasible platform on which to model the simultaneous spread and control of contagious zoonotic diseases between swine and human populations. The main limitation of this study was the lack of

empirical data on pH1N1 outbreaks in a usable form at the swine herd or household levels to calibrate a model for the evaluation of different intervention strategies. However, this study provides useful insights into the effect of strategic combinations of intervention measures, with findings that were similar to those arising from studies that modeled influenza spread in only human populations. It should be noted that this study was not intended to generate quantitative predictions; rather it attempted to provide a better qualitative assessment of the combination of control strategies.

A number of *NAADSM's* general limitations were outlined in Chapter 3. In addition, when modeling control strategies some of the limitations include: it assumes the detection is 100% specific (no false positives), no capability for tracing the contacts of detected units backward, units are quarantined permanently till the end of the simulation period, and there is no capability to assess the effects of school or workplace closure along with the quarantine of households. Imposing permanent quarantine measures for swine herds may be realistic but this is not the case for households, particularly when the duration of the outbreak is prolonged. In human studies the members of infected households have typically been quarantined for 7–21 days (Ferguson et al., 2005, Ferguson et al., 2006, Wu et al., 2006). The NAADSM version used in this study does not have a specific feature to evaluate the effectiveness of the anti-viral treatment or prophylaxis measures. The feature evaluating the ring vaccination can be used to mimic anti-viral prophylaxis by setting the delay time to immunity to one day following ring vaccination. However, this approach would mean that it would not be possible to assess

the effectiveness of the anti-viral and vaccination strategies simultaneously. In addition, ring vaccination or anti-viral treatment would be assumed to be 100% protective, which is not likely realistic.

4.6 Conclusion

This study demonstrated that effective quarantine based on the early detection of infected units alone would have the largest impact in limiting influenza outbreaks in swine populations with negligible spread to humans, given the assumptions in the model. Chapter 3 concluded the pre-emptive vaccination of swine workers was useful. In contrast, the models developed in this chapter suggest that reactive ring vaccination (up to 5 km radius), did not provide significant benefit. The modeling approach and evaluation of the effectiveness of a combination of key control strategies assessed in this study is suitable for modeling contagious zoonotic pathogens as they spread among and between animal and human populations. Furthermore, this study demonstrated that NAADSM offers a feasible and readily useable platform for such an undertaking. It is recommended that concerted efforts should be made to collect relevant information on influenza outbreaks in swine and human populations to better parameterize such models at the farm and household levels, which could greatly improve future modeling work.

4.7 References

Basta, N. E., D. L. Chao, M. E. Halloran, L. Matrajt and I. M. Longini, Jr., 2009: Strategies for pandemic and seasonal influenza vaccination of schoolchildren in the United States. Am. J. Epidemiol., 170, 679-686.

Bresson, J. L., C. Perronne, O. Launay, C. Gerdil, M. Saville, J. Wood, K. Hoschler and M. C. Zambon, 2006: Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: phase I randomised trial. Lancet, 367, 1657-1664.

Cauchemez, S., F. Carrat, C. Viboud, A. J. Valleron and P. Y. Boelle, 2004: A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. Stat. Med., 23, 3469-3487.

Dohoo, I., W. Martin and H. Stryhn, 2009: Veterinary epidemiologic research, 2 edn. VER Inc., Charlottetown, PEI, Canada.

Dorjee, S., Z. Poljak, C. W. Revie, J. Bridgland, B. McNab, E. Leger and J. Sanchez, 2012: A Review of Simulation Modelling Approaches Used for the Spread of Zoonotic Influenza Viruses in Animal and Human Populations. Zoonoses Public Hlth.

Ferguson, N. M., D. A. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn and D. S. Burke, 2005: Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature, 437, 209-214.

Ferguson, N. M., D. A. T. Cummings, C. Fraser, J. C. Cajka, P. C. Cooley and D. S. Burke, 2006: Strategies for mitigating an influenza pandemic. Nature, 442, 448-452.

Fraser, C., 2007: Estimating individual and household reproduction numbers in an emerging epidemic. PLoS One, 2, e758.

Gao, R., B. Cao, Y. Hu, Z. Feng, D. Wang, W. Hu, J. Chen, Z. Jie, H. Qiu, K. Xu, X. Xu, H. Lu, W. Zhu, Z. Gao, N. Xiang, Y. Shen, Z. He, Y. Gu, Z. Zhang, Y. Yang, X. Zhao, L. Zhou, X. Li, S. Zou, Y. Zhang, X. Li, L. Yang, J. Guo, J. Dong, Q. Li, L. Dong, Y. Zhu, T. Bai, S. Wang, P. Hao, W. Yang, Y. Zhang, J. Han, H. Yu, D. Li, G. F. Gao, G. Wu, Y. Wang, Z. Yuan and Y. Shu, 2013: Human Infection with a Novel Avian-Origin Influenza A (H7N9) Virus. N. Engl. J. Med., 368, 1888-1897.

Germann, T. C., K. Kadau, I. M. Longini, Jr. and C. A. Macken, 2006: Mitigation strategies for pandemic influenza in the United States. Proc. Natl. Acad. Sci. U. S. A., 103, 5935-5940.

Gojovic, M. Z., B. Sander, D. Fisman, M. D. Krahn and C. T. Bauch, 2009: Modelling mitigation strategies for pandemic (H1N1) 2009. Can. Med. Assoc. J., 181, 673-680.

Halloran, M. E., N. M. Ferguson, S. Eubank, I. M. Longini, Jr., D. A. T. Cummings, B. Lewis, S. Xu, C. Fraser, A. Vullikanti, T. C. Germann, D. Wagener, R. Beckman, K. Kadau, C. Barrett, C. A. Macken, D. S. Burke and P. Cooley, 2008: Modeling targeted layered containment of an influenza pandemic in the United States. Proc. Natl. Acad. Sci. U. S. A., 105, 4639-4644.

Harvey, N., A. Reeves, M. A. Schoenbaum, F. J. Zagmutt-Vergara, C. Dube, A. E. Hill, B. A. Corso, W. B. McNab, C. I. Cartwright and M. D. Salman, 2007: The North American Animal Disease Spread Model: a simulation model to assist decision making in evaluating animal disease incursions. Prev. Vet. Med., 82, 176-197.

Hill, A. and A. Reeves, 2006: User's Guide for the North American Animal Disease Spread Model, 2nd edn. Fort Collins, Colorado: Animal Population Health Institute, Colorado State University. Available at http://www.naadsm.org.

Howden, K. J., E. J. Brockhoff, F. D. Caya, L. J. McLeod, M. Lavoie, J. D. Ing, J. M. Bystrom, S. Alexandersen, J. M. Pasick, Y. Berhane, M. E. Morrison, J. M. Keenliside, S. Laurendeau and E. B. Rohonczy, 2009: An investigation into human pandemic influenza virus (H1N1) 2009 on an Alberta swine farm. Can. Vet. J., 50, 1153-1161.

Lange, E., D. Kalthoff, U. Blohm, J. P. Teifke, A. Breithaupt, C. Maresch, E. Starick, S. Fereidouni, B. Hoffmann, T. C. Mettenleiter, M. Beer and T. W. Vahlenkamp, 2009: Pathogenesis and transmission of the novel swine-origin influenza virus A/H1N1 after experimental infection of pigs. J. Gen. Virol., 90, 2119-2123.

Lee, V. J., D. C. Lye and A. Wilder-Smith, 2009: Combination strategies for pandemic influenza response - a systematic review of mathematical modeling studies. BMC Med, 7, 76.

Leroux-Roels, I., A. Borkowski, T. Vanwolleghem, M. Drame, F. Clement, E. Hons, J. M. Devaster and G. Leroux-Roels, 2007: Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial. Lancet, 370, 580-589.

Lindstrom, S., G. Rebecca, B. Amanda, S. Bo, E. Shannon, B. LaShondra, B. Nathelia, S. Katrina, G. Larisa, V. Julie and K. Alexander, 2012: Human Infections with Novel Reassortant Influenza A(H3N2)v Viruses, United States, 2011. Emerg. Infect. Dis., 18, 834-837.

Longini, I. M., A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D. A. T. Cummings and M. E. Halloran, 2005: Containing Pandemic Influenza at the Source. Science, 309, 1083-1087.

Ma, W., K. M. Lager, A. L. Vincent, B. H. Janke, M. R. Gramer and J. A. Richt, 2009: The Role of Swine in the Generation of Novel Influenza Viruses. Zoonoses Public Health, 56, 326–337.

Milne, G., J. Kelso and H. Kelly, 2009: Strategies for mitigating an influenza pandemic with pre-pandemic H5N1 vaccines. J R Soc Interface.

Myers, K. P., C. W. Olsen and G. C. Gray, 2007: Cases of swine influenza in humans: a review of the literature. Clin. Infect. Dis., 44, 1084-1088.

Myers, K. P., C. W. Olsen, S. F. Setterquist, A. W. Capuano, K. J. Donham, E. L. Thacker, J. A. Merchant and G. C. Gray, 2006: Are swine workers in the United States at increased risk of infection with zoonotic influenza virus? Clin. Infect. Dis., 42, 14-20.

NAADSM Development Team, 2008: NAADSM version number 3.1.24. Free program distributed via the Internet at http://www.naadsm.org.

Nelson, M. I., M. R. Gramer, A. L. Vincent and E. C. Holmes, 2012: Global transmission of influenza viruses from humans to swine. J. Gen. Virol., 93, 2195–2203.

Nuno, M., G. Chowell and A. B. Gumel, 2007: Assessing the role of basic control measures, antivirals and vaccine in curtailing pandemic influenza: scenarios for the US, UK and the Netherlands. J R Soc Interface, 4, 505-521.

OIE, 2013: Update on Avian Influenza. Available at: http://www.oie.int/animal-health-in-the-world/update-on-avian-influenza/2013/ (accessed 26 June 2013).

Saenz, R. A., H. W. Hethcote and G. C. Gray, 2006: Confined animal feeding operations as amplifiers of influenza. Vector Borne Zoonotic Dis., 6, 338-346.

Shaban, N., M. Andersson, A. Svensson and T. Britton, 2009: Household epidemics: modelling effects of early stage vaccination. Biom. J., 51, 408-419.

Statistics Canada, 2007: Farm Operators by Farm Type and Province (2001 and 2006 Censuses of Agriculture) (Canada) (Summary Tables). Last updated May 16, 2007. Statistics Canada:http://www40.statcan.ca/l01/cst01/agrc22a.htm?sdi=farm%20operators (Accessed on 28 March 2010).

Statistics Canada, 2007(b): Population and Dwelling Counts, for Canada, Provinces and Territories, 2006 and 2001 Censuses, 100% Data (table). “Population and dwelling count highlight tables, 2006 Census.” “2006 Census: Release topics.” Census Statistics Canada Catalogue no. 97-550-XWE2006002. Ottawa, Ontario. March 13. Statistics Canada:http://www12.statcan.gc.ca/census-recensement/2006/rt-td/pd-pl-eng.cfm/ (Accessed on 28 March 2010).

Tsai, M. T., T. C. Chern, J. H. Chuang, C. W. Hsueh, H. S. Kuo, C. J. Liau, S. Riley, B. J. Shen, D. W. Wang, C. H. Shen and T. S. Hsu Corresponding Author, 2010: Efficient simulation of the spatial transmission dynamics of influenza. PLoS Curr Influenza, RRN1141.

Tuite, A., D. N. Fisman, J. C. Kwong and A. Greer, 2010: Optimal pandemic influenza vaccine allocation strategies for the canadian population. PLoS Curr Influenza, RRN1144.

Uyeki, T. M. and N. J. Cox, 2013: Global Concerns Regarding Novel Influenza A (H7N9) Virus Infections. N. Engl. J. Med., 368, 1862-1864.

WHO, 2005: Pandemic influenza preparedness and response. Available at: http://www.who.int/influenza/resources/documents/pandemic_guidance_04_2009/en/index.html (Accessed on 26 June 2013)

WHO, 2011: Comparative analysis of national pandemic influenza. Available at: http://www.who.int/influenza/resources/documents/comparative_analysis_php_2011_en.pdf (Accessed on 26 June 2013)

Wu, J. T., S. Riley, C. Fraser and G. M. Leung, 2006: Reducing the impact of the next influenza pandemic using household-based public health interventions. PLoS Med., 3, e361-e361.

Yasuda, H. and K. Suzuki, 2009: Measures against transmission of pandemic H1N1 influenza in Japan in 2009: simulation model. Eurosurveillance, 14, 19385-19385.

Zimmer, S. M. and D. S. Burke, 2009: Historical Perspective — Emergence of Influenza A (H1N1) Viruses. N. Engl. J. Med., 361, 279-285.

Table 4.1(a): Parameters of control strategies used for simulation models of the simultaneous spread of pandemic influenza H1N1 2009 virus between swine and human populations in a county in Ontario, Canada.

Parameters		Parameter values					
		Swine herd			Household		
1. Speed of detection	Day	Slow	Moderate	Fast	Slow	Moderate	Fast
(a) Probability of observing clinical signs given the number of days that a unit is clinically infectious*	0	0	0	0	0	0	0
	1	0.1	0.4	0.7	0.1	0.4	0.8
	3	0.2	0.6	0.9	0.3	0.7	0.95
	5	0.25	0.8	0.99	0.5	0.9	0.99
	10	0.5	0.99	-	0.8	0.99	-
	15	0.9	-	-	0.9	-	-
	20	0.99	-	-	0.99	-	-
(b) Probability of reporting an observed clinical unit given the number of days since any unit was first detected *	0	0	0	0	0	0	0
	1	0.1	0.25	0.7	0.1	0.25	0.7
	3	0.5	0.6	0.9	0.5	0.6	0.9
	5	0.7	0.9	0.99	0.7	0.9	0.99
	10	0.8	0.99	-	0.8	0.99	-
	15	0.9	-	-	0.9	-	-
	20	0.99	-	-	0.99	-	-
(c) Probability of the overall detection [(a)*(b)]	0	0	0	0	0	0	0
	1	0.01	0.1	0.49	0.01	0.1	0.56
	3	0.1	0.36	0.81	0.15	0.42	0.86
	5	0.18	0.72	0.98	0.35	0.81	0.98
	10	0.4	0.98	-	0.64	0.98	-
	15	0.81	-	-	0.81	-	-
	20	0.98	-	-	0.98	-	-
2. Quarantine strategy		Radius			Radius		
(a) No-zone strategy - quarantine of detected units only (however a zone of this radius was imposed to control the indirect contacts between SH to SH, and SH to SWH, and among household units)		0.005 km			0.005 km		
(b) With-zone strategy – quarantined all units within a zone of this radius around the detected units.		3 km			3 km		
3. Effectiveness of movement control (fraction of baseline contact rate over time)	Day	Less-effective	Effective		Less-effective	Effective	
(a) Movement restriction of direct contacts of undetected units within the disease control zone (With-zone strategy only)	0	1.0	1.0		1.0§	1.0§	
	1	0.7	0.5		0.7	0.5	
	3	0.5	0.2		0.5	0.1	
	5	0.3	0.05		0.3	0.05	
	10	0.05	-		0.2	-	
(b) Movement restriction for indirect contacts upon detection for both No-zone and With-zone strategy)	0	1.0	1.0		1.0	1.0	
	1	0.7	0.5		0.7	0.5	
	3	0.5	0.3		0.5	0.1	
	5	0.3	0.05		0.3	0.05	
	10	0.2	-		0.2	-	
4. Forward contact tracing		Trace success (%)			Trace success (%)		
(a) Probability of trace success for the movement that occurred within five days of detection for direct contacts		0.95			1.0		
(b) Probability of trace success given days before the detection for indirect contacts		0.6			0.7		

*These cumulative probability distributions were converted to a daily probability distribution using spreadsheet provided by Neil Harvey of the University of Guelph and entered into the models. § This applies to the direct contacts of undetected units of swine herds (SH) and swine worker households (SWH) in with-zone strategy as the direct contacts of all the detected units were automatically quarantined with 100% effectiveness as a default setting in NAADSM. The contacts between pairs of households were simulated by indirect contact.

Table 4.1(b): Parameters of vaccination strategies used for simulation models of the simultaneous spread of pandemic influenza H1N1 2009 virus between swine and human populations in a county in Ontario, Canada

Parameters	Parameter value for both swine herds & Households		
5. Vaccination	No-vaccination	Slow-trigger	Fast-trigger
(a) Threshold level to start vaccination	-	≥5 units detected	≥25 units detected
(b) Whether to vaccinate all unit types	-	Yes	Yes
(c) Delay to immunity following vaccination of units (all units)	-	7 days	7 days
(d) Vaccine immune period	-	Permanent	Permanent
(e) Radius of the ring vaccination	-	5 km	5 km
(f) Number of units vaccinated per day (all units)	-	Day	Capacity/day
		0	20
		3	150
		5	300
		10	300

Table 4.2: Summaries of the outcomes generated from the simulation of 1,000 stochastic iterations of each scenario of the simultaneous influenza spread between swine and human populations in a county in Ontario, Canada. The figures presented are median and 5th–95th percentiles of the distributions.

Scenarios	Outbreak duration (days)	No. of units infected	
		Swine herds	Households
i. Speed of the detection			
Slow	74 (28–324)	6 (1–236)	9 (0–426)
Moderate	38 (22–66)	2 (1–7)	0 (0–7)
Fast	32 (20–46)	1 (1–3)	0 (0–3)
ii. Quarantine strategy			
No-zone (detected infected units only)	40 (21–343)	2 (1–253)	1 (0–459)
With-zone (all units within a radius of ≤3 km)	39 (21–97)	2 (1–14)	1 (0–21)
iii. Movement restriction			
Less-effective	41 (22–235)	2 (1–49)	1 (0–165)
Effective	39 (21–233)	2 (1–48)	1 (0–160)
iv. Ring vaccination (all units within ≤5 km radius)			
No ring vaccination	40 (21–296)	2 (1–190)	1 (0–377)
Slow-trigger (over 25 infected units detected)	39 (21–97)	2 (1–14)	1 (0–20)
Fast-trigger (over 5 infected units detected)	39 (22–95)	2 (1–14)	1 (0–21)

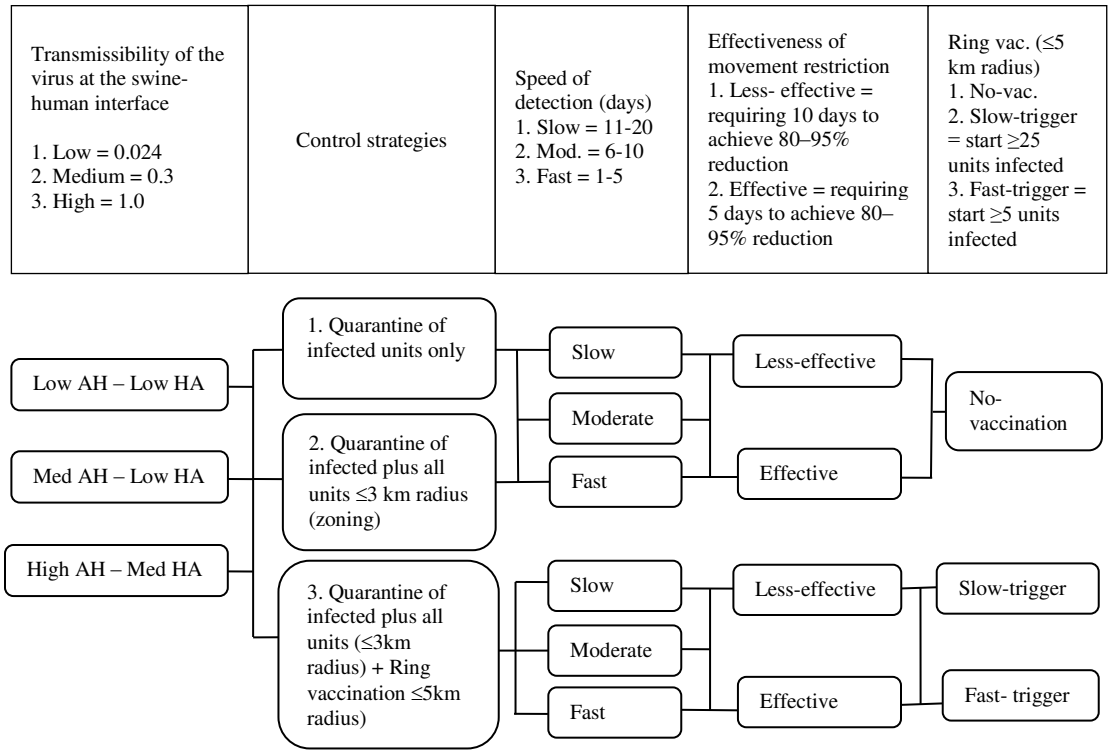

Figure 4.1: The description of scenarios used for assessing the control strategies against the simultaneous spread of pandemic influenza H1N1 2009 virus between swine and human populations in a county of Ontario, Canada. The infection was seeded in a single randomly selected swine herd. Key: AH = animal to human, HA = human to animal.

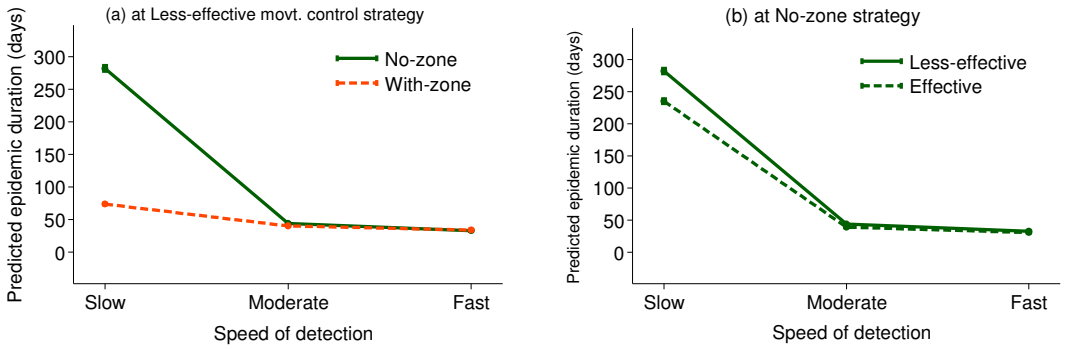

Figure 4.2: The interaction effects of control strategies on the duration of the outbreaks: (a) speed of detection and quarantine strategy, and (b) speed of detection and movement restriction strategy. The error bar shows the predicted 95% confidence intervals of the duration of the outbreak. Only the results of high animal to human – medium human to animal (HM) transmissibility of the virus are shown. Key: No-zone = quarantined the detected infected units only; With-zone = quarantined all units around the 3 km radius of the detected infected units.

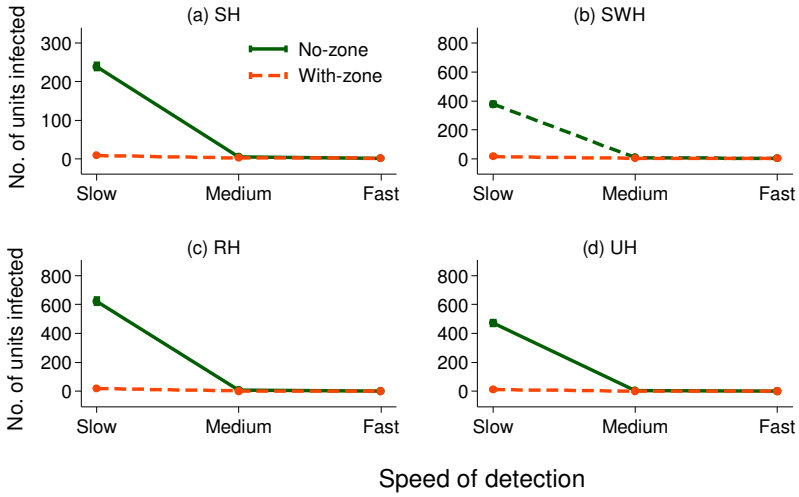

Figure 4.3: The interaction effects of speed of detection and quarantine strategy on the size of the outbreaks. The error bars show the predicted 95% confidence intervals of the size of the outbreaks. Only the results of high animal to human – medium human to animal (HM) transmissibility of the virus at the Less-effective movement restriction strategy are shown. Key: No-zone = quarantined detected infected units only, With-zone = quarantined all units within 3 km radius of the detected infected units; SH = swine herds; SWH = swine worker households; RH = rural non-swine worker households; UH = urban households.

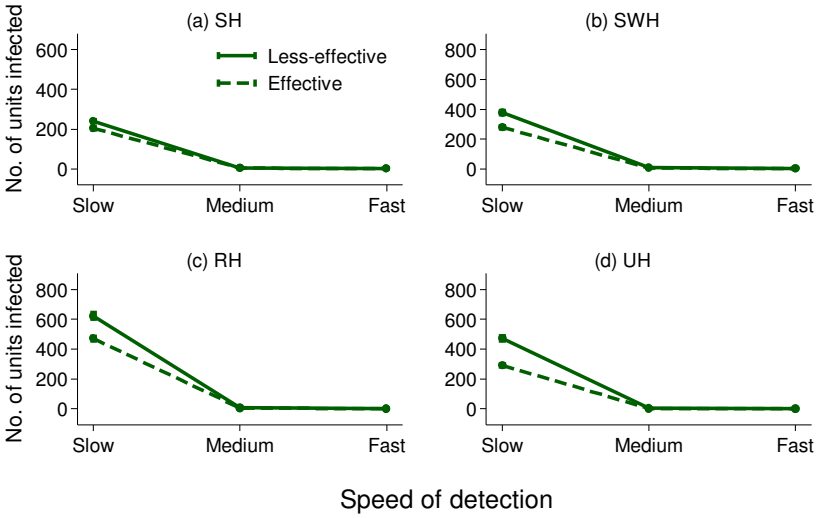

Figure 4.4: The interaction effects of speed of detection and movement restriction strategy on the size of the outbreaks. The error bars show the predicted 95% confidence intervals of the size of the outbreaks. Only the results of high animal to human – medium human to animal (HM) transmissibility of the virus at No-Zone quarantine strategy are shown. Key: (a) SH = swine herds, (b) SWH = swine worker households, (c) RH = rural non-swine worker households, (d) UH = urban households.

Chapter 5

Network Analyses of Swine Shipments in Ontario, Canada, to Support Disease Spread Modeling and Risk-based Disease Management†

† Dorjee, S., C. W. Revie, Z. Poljak, W. B. McNab and J. Sanchez, 2013: Network analysis of swine shipments in Ontario, Canada, to support disease spread modeling and risk-based disease management. Preventive Veterinary Medicine, 112, 118-127.

5.1 Abstract

Understanding contact networks is important for modeling and managing the spread and control of communicable diseases in populations. This study characterizes the swine shipment network of a multi-site production system in southwestern Ontario, Canada. Data were extracted from a company's database listing swine shipments among 251 swine farms, including 20 sow, 69 nursery and 162 finishing farms (Network A), and farms to 91 processing units (PUs - Network B) for the two-year period of 2006 to 2007. Several network metrics were generated. Network A and B were analyzed using one-mode and two-mode network methods respectively. The number of shipments per week between pairs of farms and farms to PUs ranged from 1–6 and 1–4, respectively. In network A, the medians (and ranges) of out-degree were: sow 6 (1–21), nursery 8 (0–25), and finishing 0 (0–4), over the entire two-year study period. Corresponding estimates for in-degree of nursery and finishing farms were 3 (0–9) and 3 (0–12) respectively. Outgoing and incoming infection chains (OIC and IIC), were also measured. The medians (ranges) of the monthly OIC and IIC were 0 (0–8) and 0 (0–6) respectively, with very similar measures observed for intervals of two-weeks. Nursery farms exhibited high measures of centrality. This indicates that they pose greater risks of disease spread in the network. Therefore, they should be given a high priority for disease prevention and control measures affecting all age groups alike. The Network A also demonstrated scale-free and small-world topologies as observed in other livestock shipment studies. This heterogeneity in contacts among farm types and network

topologies should be incorporated in simulation models to improve their validity. Limited results based on two-mode analysis using Network B are presented to illustrate the potential of extending the network analysis. In conclusion, this study provided useful epidemiological information and parameters for the control and modeling of disease spread among swine farms, for the first time from Ontario, Canada.

Keywords: Network analysis; swine; pigs; shipments/movement; modeling parameters

5.2 Introduction

The shipment of animals between farms is one of the main mechanisms of spread of infectious disease among livestock (Gibbens et al., 2001, Mansley et al., 2003, Kiss et al., 2006a, Ortiz-Pelaez et al., 2006, Poljak et al., 2008). Recently, network analyses have been applied to describe and quantify animal shipments between farms, and to study their implications for disease spread and control (Bigras-Poulin et al., 2006, Kiss et al., 2006b, Ortiz-Pelaez et al., 2006, Bigras-Poulin et al., 2007, Dubé et al., 2008, Kiss et al., 2008, Martinez-Lopez et al., 2009a, Vernon and Keeling, 2009, Lockhart et al., 2010, Volkova et al., 2010, Nöremark et al., 2011). Analyses of animal shipment networks help identify heterogeneity in contact frequency and the connectedness of the network. They also identify whether these contacts are permanent (for example, through trade agreements between farmers) or differ over time or distance. Knowledge of these network characteristics is useful to assess disease spread in a population (Kiss et al., 2006a, Martinez-Lopez et al., 2009b, Dubé et al., 2011, Nöremark et al., 2011).

Furthermore, it can provide guidance for targeted tracing, surveillance and disease control measures. Farms with high out-degree (number of off-farm links) can act as a key source of disease spread, whereas farms with high in-degree (number of onto-farm links) are at relatively greater risk of disease introduction since they receive shipments from many farms. Farms with both high out-degree and in-degree can act as hubs for disease spread in a network. For example, once a disease infects so called hub farms, it can spread rapidly in a scale-free network (Shirley and Rushton, 2005b, Ortiz-Pelaez et al., 2006). Strategically applying control measures at such hubs (including quarantine, vaccination or stamping out) will be more effective than similar control measures applied randomly. For risk-based surveillance, farms with low in-degree but high out-degree (low probability but high consequences) can be targeted to mitigate high impact of exotic disease introduction (Cameron, 2012). Whereas farms with high in-degree (high probability of infection) can be targeted for high surveillance sensitivity and demonstration of freedom from disease (Cameron, 2012, Frossling et al., 2012). Disease spread may be relatively slower in a small-world network, but it can spread to topologically more distant clusters and facilitate more persistent infection in the population, than in random or scale-free networks (Rahmandad and Sterman, 2008, Rahmandad et al., 2011).

Network component analyses (where components are more highly connected sub-regions of a network), have been used to estimate the likely lower and upper limits of epidemic-sizes (Bigras-Poulin et al., 2006, Kao et al., 2006, Kiss et al., 2006b, Robinson

et al., 2007). However, Dubé et al. (2008) argued that "infection chain" measures (which take into consideration the temporal sequence of livestock shipments between farms) may provide better estimates of a potential epidemic size. Furthermore, understanding animal movement networks can support regionalization and compartmentalization approaches to disease control, as encouraged by the World Organization for Animal Health (OIE). This would allow the identification of groups of regions or farms that behave as a single epidemiological unit (referred to as a compartment) in terms of risk for disease transmission, as well as risk-free groups with no links to infected groups. This can facilitate resumption or continuation of trade from disease-free regions, or even from risk-free herds within an infected region (Bigras-Poulin et al., 2007, Martinez-Lopez et al., 2009b).

Knowledge of contact networks facilitates more realism in simulation modeling of the spread and control of disease in human (Eubank et al., 2004, Longini et al., 2005, Aparicio and Pascual, 2007, Hsu and Shih, 2010, Rahmandad et al., 2011), and animal populations (Green et al., 2006, Kiss et al., 2006a, Kiss et al., 2008, Sharkey et al., 2008, Vernon and Keeling, 2009, Dubé et al., 2011). Examples of input parameters required for such models include: the number of contacts each farm has, topologies of contact networks, frequency and size of shipments, as well as movement distances between farms (Morris et al., 2001, Garner and Beckett, 2005, Harvey et al., 2007).

Pork production is a major industry in Canada. Accordingly, an outbreak of a highly contagious disease among Canadian swine would have a significant negative

socioeconomic impact. Analyses of swine shipment networks have been reported from several jurisdictions, but not yet from Canada to date (Bigras-Poulin et al., 2007, Martinez-Lopez et al., 2009a, Nöremark et al., 2011, Rautureau et al., 2012, Buttner et al., 2013). Therefore, the objectives of this study were to generate farm and network level contact measures, from the swine industry of the Province of Ontario, Canada, that are important for the development of simulation models and to support disease management strategies.

5.3 Materials and Methods

5.3.1 Study populations

Data used in this study described shipments of pigs among 251 farms (20 sow, 69 nursery and 162 finishing farms), and farms to 91 PUs (abattoirs and small-scale processing units) from January 2006 to December 2007. The study data were provided by a large swine health and management company, which serviced the above described farms, located across 15 counties in southwestern Ontario, Canada. Sow farms comprised a mixture of farrow-to-wean and farrow-to-finish operations. Nursery farms consisted of a mixture of farms rearing pigs of approximately 3–10 weeks of age (nursery) and approximately 3 weeks to market age (wean-to-finish). Finishing farms housed pigs at approximately 10 weeks to market age. Information recorded in the database included unique identity numbers (IDs) of the premises, owners, managers, and of batches of swine managed and moved as groups. In addition, shipment dates, IDs of source and destination premises, farm type, number of animals on the farms, the number

of animals in shipments, and types of animals shipped were also recorded in the database. The management company did not own any of the farms but provided health and management services, including the maintenance of swine shipment data for the swine producers. The farms were owned by 33 different owners with some owners owning multiple farms. Each farm was located on a unique land parcel and was managed by a different farm manager. Shipments of pigs from one farm to another were not limited to farms belonging to a same owner. Not all farms located in the area were serviced by this one company. Therefore, the data did not include all swine shipments during the study period, among all farms in the 15 counties. However, the data were considered to be representative of the Ontario swine industry because the vast majority of the swine farms in the province employ intensive multi-site production systems, similar to the farms managed by this company. The emphasis of this study was the network of swine movements influencing spread of disease between farms. Accordingly, a detailed analysis of the network of swine shipments from farms to abattoirs was not included.

5.3.2 Descriptive statistics

Statistics were estimated describing the number of swine-shipments per week between different farm types, and farms to PUs, for the two-year period of 2006 and 2007. Also, distributions of the sizes of farms and shipments were generated. Farm size represented the number of sows (excluding piglets), nursery or finishing pigs that a farm can

accommodate. The median value for shipment size was used in cases of multiple shipments between any specific pair of study premises.

5.3.3 Network analysis

Patterns of swine shipments among farms, and farms to PUs were characterized using network analysis (Wasserman and Faust, 1994, Newman, 2003). A network consists of collections of nodes or vertices (the unit of interest) which may or may not be connected to others by links (also known as edges or arcs). In this study, nodes represented premises (farms or PUs) and links represented shipments of pigs between source and destination premises. Links can be treated as weighted or binary depending on whether or not multiple shipments between pairs of premises are taken into consideration. Each shipment event included a batch of one or more pigs from a source to a destination premises. All links were treated as directed (arcs), involving directional shipments of pigs between premises. Since swine shipments from farms to PUs present little risk of disease spread (Bigras-Poulin et al., 2007, Nöremark et al., 2011, Rautureau et al., 2012) in comparison to farm to farm shipments, the two networks were analyzed separately. Networks can be represented as one-mode or two-mode matrix. In this study, swine shipment network among farms (Network A) was analyzed as one-mode, whereas the shipment from farms to PUs (Network B) was analyzed as two-mode network. A one-mode represent links between a same set of nodes (e.g. farm to farm contacts where rows x column matrix represents a same set of farms), and two-mode network represent

links between two different sets nodes or nodes by events (where rows and columns matrix represent two sets of entities).

5.3.3.1 One-mode network of swine shipments (Network A)

Contacts (shipments) between the 20 sow, 68 nursery and 157 finishing farms were analyzed using a one-mode directed binary network matrix. One nursery and five finishing farms that received shipments before January 2006 but shipped pigs to abattoirs only during the study period were excluded from this network. A one-mode network represents the links between the same set of entities (the row and column elements in the matrix relate to the same set of farms). In the binary network links were assigned a value of one or zero based on whether or not there was at least one shipment of pigs between a pair of farms. The intensity of off-farm (out-degree) and onto-farm (in-degree) shipments between pairs of farms were assessed by treating links as weighted, taking into consideration the number of shipments of animals between pairs of farms.

The network was characterized in terms of: (i) Network size: number of nodes, number of directed links; (ii) Farm-level centrality measures: out-degree, in-degree, betweenness, eigenvector, including normalized indices of these measures; (iii) Network-level measures: density, centralization indices of out-degree, in-degree, and betweenness, diameter, geodesic distance, clustering coefficient and fragmentation index (Wasserman and Faust, 1994). Descriptions of the network terminology used in this

paper are outlined in Table 5.1, and were based on the definitions adopted by Dubé et al., (2009), Martinez-Lopez et al., (2009b) and Newman, (2003).

5.3.3.1.1 Infection chain analysis

It has been proposed that measures referred to as the outgoing infection chain (OIC) and the incoming infection chain (IIC) are particularly relevant when considering the epidemiology of disease spread and control measures (Dubé et al., 2008; Nöremark et al., 2011). Therefore these measures were assessed in this study. OIC and IIC count all direct and indirect (contacts through other farms) off-farm and onto-farm contacts, respectively, accounting for the time sequence of shipments. These measures were generated for intervals of two-week and monthly durations, along with corresponding in-degree and out-degree measures for the same time intervals. These intervals were chosen based on the plausible range of infectious periods of most common infectious diseases and plausible lengths of a "silent phase", after an outbreak has started but before official detection occurs. For instance, an outbreak detection delay up to three weeks for foot-and-mouth disease has been reported in the literature (Keeling et al., 2001). These measures were generated using the EpiContactTrace package (version 0.6.9, http://cran.r-project.org/web/packages/EpiContactTrace) of R software version 2.15.1 (R Foundation; http://www.r-project.org).

5.3.3.1.2 Scale-free and small-world topologies

Since many networks of livestock shipments have been observed to exhibit scale-free or 'small-world' topologies (Christley and French, 2003, Webb, 2005, Bigras-Poulin et al.,

2006, Kiss et al., 2006b, Webb, 2006, Bigras-Poulin et al., 2007, Lockhart et al., 2010), the network in this study was also examined for these properties. A scale-free network is characterized by a right skewed, long-tailed, power-law distribution of the number of links (degrees) to nodes, where a large number of nodes have a few links, but a few nodes have relatively large numbers of links. Such networks are hypothesized to evolve through preferential attachment (Barabasi and Albert, 1999, Barabasi and Bonabeau, 2003). Accordingly, power-law ($P(k) \sim k^{-\gamma}$) distributions were fitted to out-degree, in-degree and total degree data, using statistical approaches described by Clauset et al., (2009). Specifically, γ and k were estimated by fitting the power law distributions to the data using maximum likelihood methods and goodness-of-fit tests based on the Kolmogorov-Smirnov (KS) statistics, where k was based on a k_{min} recommended by Clauset et al. (2009). The power-law distribution fitting and hypothesis testing were conducted using R software, including the routines: plfit.R, ConfidenceIntervals.R and GoodnessOfFit.R (available at: https://sites.google.com/site/beyondmicrofoundationscoderepo/home/r-code-repository/power-laws).

Small-world networks are characterized by clusters of nodes that are connected to each other through a few long range links. They tend to have a relatively high clustering coefficient and shorter geodesic distance than an equivalent size random network. As there is no formal statistical test for detecting small-world characteristics in a network, the clustering coefficient and geodesic distance of the observed network were compared

with a set of randomly generated networks using the equivalent number of nodes and links (Newman, 2003, Opsahl and Panzarasa, 2009). The observed network was compared with 500 Erdös-Renyi random graphs generated using the same numbers of farms and links. In the literature, a network demonstrating at least a 6-fold increase in the clustering coefficient, in comparison to the analogous random network, has been classified as small-world (Watts and Strogatz, 1998, Lockhart et al., 2010).

5.3.3.2 Two-mode network of swine shipments (Network B)

This network consisted of 209 farms (12 sow, 54 nursery and 145 finishing farms) and 91 PUs. The objectives of this analysis were to describe the number of PUs to which a farm was supplying pigs for slaughter (degree of a farm) and number of farms that a PU was receiving pigs from (degree of a PU), together with the connectedness among these farms and PUs. Furthermore, this analysis supported an assessment of differences in attributes between farms supplying pigs to large and small PUs. This two-mode undirected binary network was analyzed by converting the matrix of farms (rows) to PUs (columns) into two one-mode bipartite graphs; a farm by farm matrix with strength of links between farms representing the number of abattoirs to which farms co-supplied pigs, and a PUs by PUs matrix with strength of links between PUs representing the number of common farms from which they received pigs. On this basis, network measures such as degree, density, average geodesic distance and diameter were generated.

5.3.4 Statistical analyses

Differences in the sizes of farms and shipments among three farm types were compared using a Kruskal-Wallis (KW test) with Bonferroni post hoc adjustment for multiple comparisons. A critical value of the post hoc adjustment was calculated as $\alpha/(k*(k-1))$, where $\alpha = 0.05$ and k is the number of groups compared. For Network-A, associations between means of various network measures, including out-degree, in-degree, betweenness, and eigenvector with farm type, farm or shipment sizes, were compared using a network adapted ANOVA and t-test (for pairwise comparisons), that are based on bootstrapping and permutation approaches (Hanneman and M, 2005). These methods were used because the network measures violate the random sampling and independence assumptions, and are robust to violation of assumptions of normality and equal variance of residuals. For comparisons, farm sizes were categorized into four groups (A = 250–999; B = 1,000–1299; C = 1,300–2,099; and D = 2,100–4,000) based on 25th, 50th, and 75^{th} percentile distribution. The records of farm sizes were missing for three sow farms and two each of the nursery and finishing farms. They were estimated for these farms using a multivariate normal regression imputation method based on their respective median shipment size, out-degree, in-degree, and betweenness values. The median of 100 imputed values was used for each of these seven farms. Similarly, sizes of shipments were categorized into four groups as: A = 1–54; B = 55–100; C = 101–208; and D = 209–2,598. The numbers of relevant links identified through infection chain analysis, as compared to the number of links identified by simple degree counts, were assessed using the same two-week and monthly time intervals applied to the infection

chain analysis. Differences in two-week and monthly OIC vs. out-degree and IIC vs. in-degree measures were compared among the three farm types as well as the four groups of farm size or shipment size, using the KW test with Bonferroni post hoc adjustment described above. In addition, the distributions of both OIC and out-degree, and IIC and in-degree, were compared (for each of the two-week and monthly time intervals), using the KS goodness-of-fit test, because this test takes into consideration the whole distribution.

For Network B, a power-law distribution was fitted to degree distributions of farms and PUs, while scaling parameters were estimated as described for Network A. The associations between the degree and farm types, or farm size groups were examined using a network adapted ANOVA test. The difference in the proportion of farm size groups associated with the five largest PUs (with degree $\geq 95^{th}$ percentile) and other PUs were compared using Pearson's Chi-square test.

5.3.5 Cluster analysis

Cluster analysis was used to examine whether there were distinct groups of farms based on the farm and shipment sizes, together with key network measures (out-degree, in-degree, betweenness and eigenvector measures). Agglomerative hierarchical cluster analysis using the weighted average linkage method with a stopping rule based on the Duda and Hart index as described by Everitt et al., (2011) was used for this analysis. A Euclidean distance measure with all variables rank standardized was used for the analysis.

All network and statistical analyses, unless specified previously, were carried out using UCInet v6.360 for Windows (Borgatti et al., 2002) and Stata version 11.2 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP), respectively. For multiple comparisons using Kruskal-Wallis test, a kwallis2 package in Stata (http://fmwww.bc.edu/RePEc/bocode/k) was used. The significance of all statistical tests was assessed at the 5% significance level.

5.4 Results

5.4.1 Descriptive statistics

Descriptive statistics of swine shipments between premises are summarized in Table 5.2. Shipments from finishing to PUs accounted for 49% (6493/13177). This was followed by sow to nursery farms 28% (3690/13177), nursery to finishing farms 12% (1527/13177) while shipments from nursery to finishing farms accounted for 27% (1527/5760) of movements. Each farm shipped pigs to 1–4 other individual farms or 1–9 PUs per week. The frequency of shipments per week between pairs of farms ranged from 1–6, and from farms to PUs ranged from 1–4. Limited number of shipments between farms of the same type (nursery or finishing) were also observed. Considerable variations in the frequency of weekly and monthly shipments amongs farms were noted within each year and between the two years (Figure 5.1). The medians (ranges) of farm sizes by farm type were: sow 1200 (500–2700), nursery 2100 (450–4000) and finishing 1060 (250–2760). The farm sizes varied significantly by farm types ($P<0.001$; Figure 5.2). The distribution of shipment size also varied widely with an overall median (range)

of 101 (1–2930) pigs per shipment (Table 5.3). A significant difference in the size of shipments among the three farm types was observed with larger size shipments from nursery to finishing farms (excluding shipments from farm to PUs) ($P < 0.001$). Furthermore, a positive association between farm size groups and shipment size groups was evident (Pearson's chi-squared test P value of <0.001).

5.4.2 Network A

The network consisted of 245 farms (nodes) with 810 links. A total of 5760 shipments was observed from 147 individual sources to 211 individual destination farms. Detailed farm and network level measures are presented in Table 5.4. The overall difference in the out-degree among the three farm types was significant ($P < 0.001$). Sow and nursery farms shipped pigs to a median of six nursery and eight finishing farms, respectively (with the exception of limited shipments to other nursery farms) (Table 5.4). The difference in out-degrees between these two farm types was not statistically significant (when assessed against a post hoc test's critical value). Except for the 63 finishing farms that shipped pigs to 1–4 other finishing farms, most finishing farms (94) shipped pigs only to PUs. Since those shipments to PUs were excluded from the analysis, most finishing farms had out-degrees of zero in this network of farm-to-farm animal shipments. Similarly, three nursery farms were wean-to-finish farms (sent shipments off-farms only to abattoirs) and therefore had out-degrees of zero for this network. Significant positive associations between out-degree and farm size groups and shipment size groups were evident ($P<0.001$; Figure 5.3).

The difference of in-degree distributions between nursery and finishing farms was not significant (when assessed against a post hoc test's critical value). In-degree values presented a borderline signficant association with farm size groups (P = 0.055), but they had a significant association with the shipment size groups (P <0.001; Figure 5.4). None of the sow, eight nursery and six finishing farms in this data received any shipments (in-degress of zero). Most of these farms sourced replacements from within their own farms, but some may have had other sources who were not clients of the swine management company involved in this study and were therefore not included in the study data.

Yearly network measures were also estimated (but not provided in Table 5.4). The overall median (range) of out-degree values for both the yearly networks was 0 (0–15), and the in-degree values were 2 (0–7) and 2 (0–8) for 2006 and 2007, respectively. Sow and nursery farms had similar values of out-degree with an overall median (range) of 4 (0–15) for the yearly networks (not including shipments from finishing farms to abattoirs). The in-degree values for the nursery and finishing farms were similar, with an overall median (range) of 2 (0–8). The medians (ranges) of the overall total-degree of 2006 and 2007 yearly networks were 4 (1–17) and 4 (1–18), respectively.

Only nursery and finishing farms had betweenness centrality scores greater than zero. In particular, four nursery farms had the highest betweenness score of 93 (farm K), 102 (farm J), 104 (farm D), and 106 (farm G) (Figure 5.5 (b)). These farms also had relatively high out-degree, in-degree and eigenvector scores (Figure 5.5 (a) and (b)). The

betweenness scores of nursery farms were significantly higher than for finishing farms ($P < 0.001$). Betweenness scores were significantly associated with farm size and shipment size groups ($P < 0.001$; Figure 5.6).

No significant differences in eigenvector scores among farm types or farm size groups were observed (P value of 0.121 and 0.163, respectively; Figure 5.7 (a)). However, eigenvector scores differed significantly among shipment size groups ($P < 0.001$; Figure 5.7 (b)). A plot of eigenvector and betweenness scores shown in Figure 5.5 (b) identified key farms with high scores of these measures, indicating their influential role in the flow of swine shipments among the farms.

5.4.2.1 Cluster analysis

Cluster analysis identified five clusters (Table 5.5). Cluster #1 included a range of farm characteristics. Cluster #2 consisted primarily of finishing farms with high in-degree, small farm and shipment sizes, and the lowest out-degree, betweenness, and eigenvector scores. Cluster #3 consisted of an equal proportion of sow and nursery farms with large farm size, intermediate values of shipment size, out-degree, betweenness and eigenvector scores, and lowest in-degree. Cluster #4 consisted of only nursery farms with the highest out-degree, betweenness and eigenvector scores and largest farm and shipment sizes, and relatively high in-degree (see Figure 5.5 (a) and (b)). Cluster #5 consisted of a single nursery farm with the largest shipment size and larger farm sizes, but with lowest network measures.

5.4.2.2 Infection chain analysis

The medians for each of the OIC, IIC, out-degree and in-degree measures, were not significantly different within each measure-type, based on two-week vs. one-month time intervals. However, the maximum values of out-degree, IIC and OIC, were higher for monthly vs. two-week intervals. Accordingly, for brevity, only results for the monthly network measures are presented here. The overall medians (ranges) of monthly measures were: out-degree 0 (0–7), OIC 0 (0–8), in-degree 0 (0–5), and IIC 0 (0–6). These measures differed significantly among farm types ($P < 0.001$). Sow farms had relatively higher out-degree and OIC with median (range) values of 2 (0–7) and 3 (0–8) respectively, and zero in-degree and IIC. The median values of all these measures were zero for both nursery and finishing farms. However, the nursery farms had relatively higher ranges of out-degree (0–5) and the OIC (0–6) than the finishing farms (out-degree of 0–2; OIC of 0–3). While the nurseries had higher in-degree range (0–5) than finishing farms (0–3), IIC range was lower for nursery (0–5) than finishing farms (0–6). The percentages of three farm types likely to have ranges of monthly OIC and IIC are shown in Figure 5.8 (a) and (b), respectively. It shows that 88% of the sow farms, 36% of the nursery and 4% of the finishing farms shipped pigs to at least one farm in a month (Figure 5.8 (a)). Similarly, 39% of the nursery and 21% of the finishing farms received pigs from at least one farm in a month (Figure 5.8 (b)). No differences in these measures were observed between 2006 and 2007 years ($P > 0.05$). Significant positive

associations between monthly OICs or IICs measures with farm size groups or shipment size groups were evident (all $P < 0.0001$).

5.4.2.3 Scale-free topology

The out-degree and in-degree distributions had power law scaling parameters (γ) of 1.97 (95% CI 1.82–2.14) and 4.34 (95% CI 3.65–5.15) for farms with the out- and in-degree >2 and >6, respectively. There were 147 and 79 farms above these threshold limits, respectively. The total degree distribution had a power law scaling exponent (γ) of 2.69 (95% CI 2.40–3.02) for farms with the degree >6 (consisted of 116 farms). The KS test failed to reject the power law model as a plausible model for out-degree and total degree ($P>0.05$). However, this test was significant for the in-degree distribution ($P < 0.001$).

5.4.2.4 Network-level measures

In general, the network density and clustering coefficient were low. The high fragmentation index indicated that the proportion of unreachable pairs of farms was high in the network. The network's out-degree, in-degree and betweenness centralization indices were also low, illustrating a relatively low reliance or concentration of off- and onto-farms shipments from/to a few nodal farms at the macro-level of the entire network. A median geodesic distance of two indicates the presence of only one farm on the most efficient pathway between any two farms in general.

5.4.2.5 Small-world topology

The overall median geodesic distance of 500 simulated random graphs of equivalent network size of the observed network was 5 with the overall median (5^{th} and 95^{th} percentiles) of clustering coefficient of 0.013 (0.011–0.012). The relatively shorter geodesic distance (two) and larger clustering coefficient (0.09) of the observed network compared with random graphs of equivalent size demonstrated small-world topology of the swine shipment network. A network graph showing farms, where the size of the nodes was made proportional to the total degree is shown in Figure 5.9.

5.4.3 Network B

The descriptive metrics of Network B are presented in Table 5.6. There was high heterogeniety in the degree distributions of both farms and PUs. The degree distributions for both farms and PUs followed a power-law distribution with scaling exponent (γ) of 3.63 (95% CI 3.23–4.07) and 1.98 (95% CI 1.74–2.27) at minimum degree thresholds over three and two respectively. There were 160 farms and 55 PUs with a degree value above these threshold limits. The KS test failed to reject the power law as a plausible model in both the cases with $P > 0.05$. Three PUs (main abattoirs) had the highest degree of 129, 134, and 144 respectively, which was evident from the two-mode network graph shown in Figure 5.10. No significant differences in the degree amongst the three farm types or farm size groups were evident (P value of 0.202 and 0.1046 respectively). A significant positive association between the size of the farms

supplying pigs to PUs with the 5 highest degree values compared with farms supplying to other PUs was evident ($P<0.001$).

5.5 Discussion

This study described the network characteristics of swine shipments among 245 farms, in 15 counties, in the province of Ontario, Canada. As a non-random sample, the study data were not fully representative of all swine farms in Ontario (Statistics Canada, 2007). However, it did include swine shipment events over a two-year period, from 13% (251/1950) of swine farms in 15 of 47 swine rearing counties, or 6.2% (251/4070) of all swine farms in Ontario (Statistics Canada, 2007). The majority of Ontario swine farms participate in multi-site production systems, where individual farms specialize in a specific production type (breeder, farrow-to-wean, nursery, or finishing). As in most developed countries, Canadian and Ontario swine production chains follow pyramidal structures, where a few farms higher up in the production chain supply pigs to a larger number of farms down the chain (Bigras-Poulin et al., 2007, Clauset et al., 2009, Nöremark et al., 2011, Buttner et al., 2013). Most of these farms also operate under a single integrator or on the basis of fairly permanent trade partnerships, where a farrowing farm supplies a specific, relatively fixed set of nursery farms, etc. Thus data obtained for this study described a sub-network, within the overall network of swine shipments in Ontario. Considering this farming structure, we can assume that estimates of farm-level centrality measures of this network represent reasonable estimates of the typical commercial multi-site production systems in Ontario. Furthermore, since these

data captured all swine shipments of participating farms, including those shipments to and from farms outside the enrolment of this company (except for the supply of replacement sows), the magnitude of bias in the farm-level measures are likely small. However, network level measures observed in this study, such as density and fragmentation indices will be subject to some degree of bias, because such measures depend on the total number of farms present in the network. In addition, given that number of farms and animals in these 15 counties remained stable between 2006 (farms = 1950 and animals = 3.4 million) and 2011 (farms = 1703 and animals = 2.7 million) these estimates may not have been affected much even though data was about 5–6 years old (Statistics Canada, 2007, Statistics Canada, 2012).

This study provided useful preliminary information on the characteristics of multi-site commercial swine shipment networks in Ontario. It illustrated the types of farms that tend to be more centrally connected and could thus guide the prioritization of control measures, and provide some indication of the potential size of epidemics in such networks. It also provided preliminary parameters required for modeling disease spread among swine farms, such as contact frequencies, the number of links between farms, and the structure of network topologies. As a caution, the network statistics observed during normal trading may change once quarantines or movement controls are implemented during the outbreak response phase (Shirley and Rushton, 2005a).

The frequency of off-farm shipments per week (ranging from 1–6, Table 5.2), can be used as input parameter for the contact rate in simulation models. However, such simple

statistics are much more informative when combined with the network information such as: the number of links over which those shipments occur, which types of nodes are involved, or the contact structure of the network.

The high and similar out-degree distributions observed for sow and nursery farms compared with finishing farms illustrated the similar risk these two farm-types present as disease sources, once they become infected. However, when one also considers the higher in-degree of nursery farms (relative to sow farms), it is clear that nursery farms present a greater overall risk through their ability to act as hubs in the spread of disease. The out-degree of finishing farms (links to other finishing farms) was very low in this particular dataset. However, some finishing farms also ship gilts to sow farms in Ontario, was also reported in other countries (Bigras-Poulin et al., 2006, Buttner et al., 2013)**.** In general, finishing farms may present a lower risk to the spread of disease from farm-to-farm by animal shipments. The similar in-degree distributions of nursery and finishing farms implied similar vulnerability to, or risk of, introduction (receipt) of diseased animals. However once again, considering the higher out-degree of nursery farms, they will likely be more influential in the spread of disease in the network. The out-degree measures of sow and finishing farms, and in-degree measure of finishing farms in this study were similar to those observed by Buttner et al. (2013). This re-enforces the fact that these data, despite being based on a relatively small network, can provide useful information when estimating farm-level measures of centrality.

Their higher betweenness scores means that targeting nursery farms for disease control measures can be more effective and efficient at the network population level (although this may be infection-specific and nursery-specific) than similar controls applied to sow or finishing farms. The eigenvector scores for individual farms provided additional insights into their respective centrality, because this score is weighted by the centrality scores of farms connected to the farm being assessed. Farms with both high betweennesss and high eigenvector scores are certainly hubs that will likely act as 'super-spreaders' if infected. In this study, all such farms were observed to be nursery farms (Figure 5.5 (b)) and belonged to a single Cluster#4. Farms with high betweenness and low eigenvector scores act as central bridges connecting farms to the core of a network, which would otherwise be isolated. Removing these farms from the network increases the fragmentation index of a network. Farms with low betweenness scores but high eigenvector are well-connected and lie at the core of the network, but they have very few connections outside the core region. Identifying such farms can be useful for disease surveillance and disease outbreak management.

The positive associations observed for farm-size and shipment-size, with out-degree, and measures of centrality indicated that, in addition to large farms receiving and making more shipments to more farms, the probability of at least one infected animal being included in any of those shipments is greater for any given prevalence of disease within the source herd at the time. Some of the disease spread modeling tools explicitly model the disease transmission probability per shipment as a function of farm size,

within-farm prevalence of an infection, and shipment size (Morris et al., 2001, Aparicio and Pascual, 2007, NAADSM Development Team, 2011). It should be cautioned that other factors such as the biology of the disease agent, biosecurity and management practices of farms and other factors governing between-farm linkages should also be considered in estimating the overall risk of disease transmission.

Cluster analysis provided a useful holistic picture of important aspects of the network. Most notably, it identified a group of specific nursery farms (cluster #4) with combined characteristics of large farm and shipment sizes and high measures of centrality. Given that individual farm characteristics may change over time (e.g. farm size, shipment size, frequency or degrees); if contemporary farm-specific data of such characteristics are not available at the time of an outbreak, then a reasonable precautionary policy would be to give higher priority to nursery farms in general, as targets for control measures.

Normally infection chains analyses (OIC and IIC) are used for contact tracing during response to an outbreak of an emerging disease. However, knowledge of the characteristics of infection chains in a given network, before an outbreak, is also useful. Such knowledge can be used to prepare for and mitigate an outbreak, as well as estimate its likely magnitude, before an outbreak even starts. This is because infection chain analyses take into account direct and series contacts (through other farms), and the temporal sequence of these contacts (Dubé et al., 2008, Nöremark et al., 2011). Estimates of the OIC and IIC of two-week and monthly interval networks were similar

to out-degree and in-degree estimates in this study. This suggested that estimates based simply on out-degree and in-degree provide an equivalent estimate of the likely magnitude of disease spread for a duration of up to one month. Since sow farms had significantly higher OIC than other farm types, the consequence component of the risk of disease spread from sow farms was higher than for other farm types. Similarly, since finishing farms had significantly higher IIC, the risk of them becoming infected was greater than for other farm types. Thus, farms with high IIC can be targeted for surveillance to increase the probability of detecting the infection, relative to random surveillance sampling of the population (Nöremark et al., 2011, Frossling et al., 2012, Rautureau et al., 2012, Buttner et al., 2013).

The scale-free topology of the network observed here was consistent with the findings of other studies of livestock shipments (Bigras-Poulin et al., 2007, Dubé et al., 2008, Lockhart et al., 2010, Nöremark et al., 2011, Rautureau et al., 2012, Buttner et al., 2013). This scale-free topology indicated that the degree distributions of farms were heterogeneous and that hubs (highly connected farms) were present. Knowledge of the scale-free topology and highly connected farms is useful for prioritizing risk-based surveillance, tracing and control measures (Martinez-Lopez et al., 2009b, Dubé et al., 2011). It is particularly important because the speed of disease spread is faster in scale-free than in non-scale-free networks due to the presence of 'super-spreaders' (Shirley and Rushton, 2005b, Rahmandad and Sterman, 2008). Also, the speed of detection and control is faster if one takes into account the scale-free nature of the network by

targeting hubs, than if only random surveillance and routine contact tracing is used to control an outbreak in a scale-free network (Shirley and Rushton, 2005b, Kiss et al., 2006a, Dube et al., 2011). The power-law scaling exponent for the total degree in this study was similar to other studies (Bigras-Poulin et al., 2007, Rautureau et al., 2012, Buttner et al., 2013). The out-degree and the scaling exponent are important parameters required for constructing a realistic scale-free network structure for network-based disease spread simulation models. For example, a median number of 4 off-farm links per farm (based on the yearly networks) along with the scaling exponent of 1.97 (95% CI 1.82–2.14) could be used to construct a scale-free network for simulating disease spread over a one-year duration.

Low density and low clustering coefficient, and high fragmentation index of swine shipments networks in general indicate that the likelihood of a disease spreading to every farm may be relatively low, assuming swine shipments between farms alone drives a disease spread. The small-world properties observed in this network indicated the presence of localized clusters that were connected to topologically distant clusters through a few long range connections. This kind of topology makes it possible for a disease to spread between distant clusters in the network. Small-world properties observed in this network were consistent with those reported in swine (Nöremark et al., 2011, Rautureau et al., 2012) and other livestock species (Leon et al., 2006, Dubé et al., 2008, Lockhart et al., 2010).

Although, swine shipment from farms to PUs presents little risk of disease transmission to other farms (Nöremark et al., 2011, Rautureau et al., 2012), analysis of such networks can provide useful information. As many surveillance protocols for animal diseases, including zoonotic diseases, are implemented at abattoir level, analysis of such information elucidates the extent to which various farms that may be involved in the case of detection of a disease at an abattoir. Subsequently, differences in farm-level risk factors such as biosecurity measures and other management factors can be compared between groups of farms supplying pigs to case abattoirs (an abattoir where a particular disease has been detected) and non-case abattoirs. This may also facilitate traceability of a disease to source farms. Wide ranges in the degree of farms and PUs were observed in this study since PUs included sales to small-scale butcher shops as well as to the large PUs.

5.5.1 General comments

These results should be extrapolated cautiously. Nevertheless, this study provided epidemiologically relevant and reasonable estimates of farm-level measures, particularly for southwestern counties of Ontario. Future studies should consider incorporating indirect contacts and shipment distances between farms as these are important parameters to consider in spatially-explicit diseases spread models (Morris et al., 2001, Garner and Beckett, 2005, Green et al., 2006, Harvey et al., 2007).

5.6 Conclusion

This study provided insights into a large swine shipment contact network in southwestern Ontario in Canada. Nursery farms are the high-risk farms in terms of risk of disease introduction as well as a potential source of spread to other farms (for infectious diseases that affect all age groups alike), and should be accorded high priority for disease prevention and control measures. The study found heterogeneity in the frequency of contacts among farm types. Also the network demonstrated small-world and scale-free topologies, consistent with livestock shipment networks reported in several other countries. Any attempt to incorporate disease transmission dynamics within simulation models should take these into consideration.

5.7 References

Aparicio, J. P. and M. Pascual, 2007: Building epidemiological models from R0: an implicit treatment of transmission in networks. Proc. Biol. Sci., 274, 505-512.

Barabasi, A. L. and R. Albert, 1999: Emergence of scaling in random networks. Science, 286, 509-512.

Barabasi, A. L. and E. Bonabeau, 2003: Scale-free networks. Sci. Am., 288, 60-69.

Bigras-Poulin, M., K. Barfod, S. Mortensen and M. Greiner, 2007: Relationship of trade patterns of the Danish swine industry animal movements network to potential disease spread. Prev. Vet. Med., 80, 143-165.

Bigras-Poulin, M., R. A. Thompson, M. Chriel, S. Mortensen and M. Greiner, 2006: Network analysis of Danish cattle industry trade patterns as an evaluation of risk potential for disease spread. Prev. Vet. Med., 76, 11-39.

Borgatti, S. P., M. G. Everett and L. C. Freeman, 2002: UCInet 6.0 Version 3.60 for Windows: Software for Social Network Analysis. Havard: Analytic Technologies.

Buttner, K., J. Krieter, A. Traulsen and I. Traulsen, 2013: Static network analysis of a pork supply chain in Northern Germany-Characterisation of the potential spread of infectious diseases via animal movements. Prev. Vet. Med., 110, 418-428.

Cameron, A. R., 2012: The consequences of risk-based surveillance: Developing output-based standards for surveillance to demonstrate freedom from disease. Prev. Vet. Med., 105, 280-286.

Christley, R. M. and N. P. French, 2003: Small-world topology of UK racing: the potential for rapid spread of infectious agents. Equine Vet. J., 35, 586-589.

Clauset, A., C. Shalizi and M. Newman, 2009: Power-law distributions in empirical data. SIAM Review, 51, 661-703.

Dube, C., C. Ribble, D. Kelton and B. McNab, 2011: Estimating potential epidemic size following introduction of a long-incubation disease in scale-free connected networks of milking-cow movements in Ontario, Canada. Prev. Vet. Med., 99, 102-111.

Dubé, C., C. Ribble, D. Kelton and B. McNab, 2008: Comparing network analysis measures to determine potential epidemic size of highly contagious exotic diseases in fragmented monthly networks of dairy cattle movements in Ontario, Canada. Transbound Emerg Dis, 55, 382-392.

Dubé, C., C. Ribble, D. Kelton and B. McNab, 2009: A review of network analysis terminology and its application to foot-and-mouth disease modelling and policy development. Transbound Emerg Dis, 56, 73-85.

Dubé, C., C. Ribble, D. Kelton and B. McNab, 2011: Introduction to network analysis and its implications for animal disease modelling. Rev. Sci. Tech., 30, 425-436.

Eubank, S., H. Guclu, V. S. Anil Kumar, M. V. Marathe, A. Srinivasan, Z. Toroczkai and N. Wang, 2004: Modelling disease outbreaks in realistic urban social networks. Nature, 429, 180-184.

Everitt, B. S., S. Landau, M. Leese and D. Stahl, 2011: Cluster Analysis, 5th ed edn. John Wiley & Sons Ltd, Chichester, West Sussex, UK.

Frossling, J., A. Ohlson, C. Bjorkman, N. Hakansson and M. Noremark, 2012: Application of network analysis parameters in risk-based surveillance - examples based on cattle trade data and bovine infections in Sweden. Prev. Vet. Med., 105, 202-208.

Garner, M. G. and S. D. Beckett, 2005: Modelling the spread of foot-and-mouth disease in Australia. Aust. Vet. J., 83, 758-766.

Gibbens, J. C., C. E. Sharpe, J. W. Wilesmith, L. M. Mansley, E. Michalopoulou, J. B. Ryan and M. Hudson, 2001: Descriptive epidemiology of the 2001 foot-and-mouth disease epidemic in Great Britain: the first five months. Vet. Rec., 149, 729-743.

Green, D. M., I. Z. Kiss and R. R. Kao, 2006: Modelling the initial spread of foot-and-mouth disease through animal movements. Proc. Biol. Sci., 273, 2729-2735.

Hanneman, R. and R. M, 2005: Introduction to social network methods. Published in digital form at http://faculty.ucr.edu/~hanneman/. Riverside, CA: University of California (accessed on 10 July 2012).

Harvey, N., A. Reeves, M. A. Schoenbaum, F. J. Zagmutt-Vergara, C. Dube, A. E. Hill, B. A. Corso, W. B. McNab, C. I. Cartwright and M. D. Salman, 2007: The North American Animal Disease Spread Model: a simulation model to assist decision making in evaluating animal disease incursions. Prev. Vet. Med., 82, 176-197.

Hsu, C. I. and H. H. Shih, 2010: Transmission and control of an emerging influenza pandemic in a small-world airline network. Accid. Anal. Prev., 42, 93-100.

Kao, R. R., L. Danon, D. M. Green and I. Z. Kiss, 2006: Demographic structure and pathogen dynamics on the network of livestock movements in Great Britain. Proc. Biol. Sci., 273, 1999-2007.

Keeling, M. J., M. E. Woolhouse, D. J. Shaw, L. Matthews, M. Chase-Topping, D. T. Haydon, S. J. Cornell, J. Kappey, J. Wilesmith and B. T. Grenfell, 2001: Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape. Science, 294, 813-817.

Kiss, I. Z., D. M. Green and R. R. Kao, 2006a: Infectious disease control using contact tracing in random and scale-free networks. J. R. Soc. Interface, 3, 55-62.

Kiss, I. Z., D. M. Green and R. R. Kao, 2006b: The network of sheep movements within Great Britain: Network properties and their implications for infectious disease spread. J. R.Soc. Interface, 3, 669-677.

Kiss, I. Z., D. M. Green and R. R. Kao, 2008: The effect of network mixing patterns on epidemic dynamics and the efficacy of disease contact tracing. J R Soc Interface, 5, 791-799.

Leon, E. A., M. A. Stevenson, S. J. Duffy, M. Ledesma and R. S. Morris, 2006: A description of cattle movements in two departments of Buenos Aires province, Argentina. Prev. Vet. Med., 76, 109-120.

Lockhart, C. Y., M. A. Stevenson, T. G. Rawdon, N. Gerber and N. P. French, 2010: Patterns of contact within the New Zealand poultry industry. Prev. Vet. Med., 95, 258-266.

Longini, I. M., Jr., A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D. A. Cummings and M. E. Halloran, 2005: Containing pandemic influenza at the source. Science, 309, 1083-1087.

Mansley, L. M., P. J. Dunlop, S. M. Whiteside and R. G. Smith, 2003: Early dissemination of foot-and-mouth disease virus through sheep marketing in February 2001. Vet. Rec., 153, 43-50.

Martinez-Lopez, B., A. M. Perez and J. M. Sanchez-Vizcaino, 2009a: Combined application of social network and cluster detection analyses for temporal-spatial characterization of animal movements in Salamanca, Spain. Prev. Vet. Med., 91, 29-38.

Martinez-Lopez, B., A. M. Perez and J. M. Sanchez-Vizcaino, 2009b: Social network analysis. Review of general concepts and use in preventive veterinary medicine. Transbound Emerg Dis, 56, 109-120.

Morris, R. S., J. W. Wilesmith, M. W. Stern, R. L. Sanson and M. A. Stevenson, 2001: Predictive spatial modelling of alternative control strategies for the foot-and-mouth disease epidemic in Great Britain, 2001. Vet. Rec., 149, 137-144.

NAADSM Development Team, 2011: NAADSM version number 4.0.11. Free program distributed via the Internet at http://www.naadsm.org.

Newman, M. E. J., 2003: The Structure and Function of Complex Networks. SIAM Review, 45, 167-256.

Nöremark, M., N. Hakansson, S. S. Lewerin, A. Lindberg and A. Jonsson, 2011: Network analysis of cattle and pig movements in Sweden: measures relevant for disease control and risk based surveillance. Prev. Vet. Med., 99, 78-90.

Opsahl, T. and P. Panzarasa, 2009: Clustering in weighted networks. Soc Networks, 31, 155-163.

Ortiz-Pelaez, A., D. U. Pfeiffer, R. J. Soares-Magalhaes and F. J. Guitian, 2006: Use of social network analysis to characterize the pattern of animal movements in the initial phases of the 2001 foot and mouth disease (FMD) epidemic in the UK. Prev. Vet. Med., 76, 40-55.

Poljak, Z., C. E. Dewey, S. W. Martin, J. Christensen, S. Carman and R. M. Friendship, 2008: Prevalence of and risk factors for influenza in southern Ontario swine herds in 2001 and 2003. Can. J. Vet. Res., 72, 7-17.

Rahmandad, H., K. Hu, R. J. Duintjer Tebbens and K. M. Thompson, 2011: Development of an individual-based model for polioviruses: implications of the selection of network type and outcome metrics. Epidemiol. Infect., 139, 836-848.

Rahmandad, H. and J. Sterman, 2008: Heterogeneity and Network Structure in the Dynamics of Diffusion: Comparing Agent-Based and Differential Equation Models. Manage. Sci., 54, 998–1014.

Rautureau, S., B. Dufour and B. Durand, 2012: Structural vulnerability of the French swine industry trade network to the spread of infectious diseases. Animal, 6, 1152-1162.

Robinson, S. E., M. G. Everett and R. M. Christley, 2007: Recent network evolution increases the potential for large epidemics in the British cattle population. J. R. Soc. Interface, 4, 669-674.

Sharkey, K. J., R. G. Bowers, K. L. Morgan, S. E. Robinson and R. M. Christley, 2008: Epidemiological consequences of an incursion of highly pathogenic H5N1 avian influenza into the British poultry flock. Proc. Biol. Sci., 275, 19-28.

Shirley, M. D. and S. P. Rushton, 2005a: Where diseases and networks collide: lessons to be learnt from a study of the 2001 foot-and-mouth disease epidemic. Epidemiol. Infect., 133, 1023-1032.

Shirley, M. D. F. and S. P. Rushton, 2005b: The impacts of network topology on disease spread. Ecol. Complexity, 2, 287-299.

Statistics Canada, 2007: Farm operators by farm type and province (2001 and 2006 Censuses of Agriculture) (Canada) (Summary Tables). Last updated May 16, 2007. Statistics Canada:http://www40.statcan.ca/l01/cst01/agrc22a.htm?sdi=farm%20operators (Accessed on 28 March 2010).

Statistics Canada, 2012: 2011 Census of Agriculture: Farm and farm operator data. Statistics Canada:http://www.statcan.gc.ca/ca-ra2011/index-eng.htm (Accessed on 9 May 2013).

Vernon, M. C. and M. J. Keeling, 2009: Representing the UK's cattle herd as static and dynamic networks. Proc. Biol. Sci., 276, 469-476.

Volkova, V. V., R. Howey, N. J. Savill and M. E. Woolhouse, 2010: Sheep movement networks and the transmission of infectious diseases. PLoS One, 5, e11185.

Wasserman, S. and K. Faust, 1994: Social Network Analysis, Methods and Applications. Cambridge University Press, New York.

Watts, D. J. and S. H. Strogatz, 1998: Collective dynamics of 'small-world' networks. Nature, 393, 440-442.

Webb, C. R., 2005: Farm animal networks: unraveling the contact structure of the British sheep population. Prev. Vet. Med., 68, 3-17.

Webb, C. R., 2006: Investigating the potential spread of infectious diseases of sheep via agricultural shows in Great Britain. Epidemiol. Infect., 134, 31-40.

Table 5.1: Description of network terminology used in the main text.

Terminology	Description
Betweenness	The number of times that a node falls on the shortest path between other pairs of nodes in the network.
Betweenness centralization index	The sum of differences between largest betweenness of most central node with all other nodes divided by the maximum possible values, and expressed in percentage terms.
Clustering coefficient	The proportion of closed triplets out of the total number of triplets (both open and closed) present in the network. A triplet is formed when three nodes are connected by either two (open triplets) or three (closed triplets) undirected links (Opsahl and Panzarasa, 2009).
Density	Density is the proportion of links (L) present out of all possible links in the network. For a directed network density is equal to L/(N(N-1)), where N is the number of nodes present.
Diameter	The longest geodesic distance between any pair of nodes of a network.
Eigenvector	A relative centrality score of a node assigned as an increasing function of the sum of all the centralities of all the nodes to which it is connected. A node connected to other nodes with high centrality scores will have higher Eigenvector score than another node with equal connections, but connected to nodes with low centrality scores. Therefore this measure not only accounts for a node's degree but also for the degree of the other nodes to which it is connected.
Fragmentation	The proportion of pairs of nodes in a network that are unreachable either through direct or indirect pathways and provide measure of network's disconnectedness.
Geodesic distance	The shortest possible path between two nodes and is the most efficient connection between them.
In-degree	In the directed network, in-degree is the number of nodes from which a particular node received shipments of animals. For weighted directed network, in-degree represents number of shipments received by a node irrespective of the node from which the shipment originated.
In-degree centralization index	The sum of the differences between largest in-degree of most central node with all other nodes divided by the maximum possible values and expressed in percentage.
Links	The connection between pairs of nodes established through shipments of animals.
Network size	The total number of possible unique pairs of nodes. If N is equal to the number of nodes, then network size is equal to N (N-1).
Normalized betweenness	The proportion of betweenness of a node to a maximum possible betweenness of the network and expressed in percentage.
Normalized in-degree	It is the in-degree of a node divided by the maximum possible degree of the network and expressed in percentage.
Normalized out-degree	It is the out-degree of a node divided by the maximum possible degree of the network and expressed in percentage.
Nodes/vertices	Premises such as farms and PUs in the network.
Out-degree	In the directed network, out-degree of a node is the number of out-going links to other nodes (number of premises to which a farm sent its swine shipments). In a weighted directed network, out-degree of a node is the number of shipments sent to other premises.
Out-degree centralization index	The sum of the differences between largest out-degree of most central node with other nodes divided by the maximum possible values, and expressed in percentage.

Table 5.2: Descriptive statistics of swine shipments among farms, and farms to processing units (PUs) for 2006 and 2007 in southwestern Ontario, Canada.

Farm type		No. of source farms		No. of destination farms		Total no. of links		Total no. of shipments		Median (range) of weekly off-farm links	Median (range) of weekly shipments/ pair
Source	Destination	2006	2007	2006	2007	2006	2007	2006	2007		
Sow	Nursery	19	20	47	47	121	113	1787	1903	1 (1–3)	2 (1–6)
Sow	PUs	12	8	5	3	23	8	112	86	1 (1)	1 (1–2)
Nursery	Nursery	21	39	20	36	23	51	26	82	1 (1)	1 (1)
Nursery	Finishing	46	46	107	110	295	294	696	831	1 (1–4)	1 (1–3)
Nursery	PUs	46	44	37	17	143	101	325	401	1 (1–3)	1 (1–3)
Finishing	Finishing	49	57	48	61	61	89	232	203	1 (1–2)	1 (1–6)
Finishing	PUs	109	118	56	55	373	407	3158	3335	1 (1–9)	1 (1–4)

Table 5.3: Distribution of the number of pigs shipped by premises types for the period 2006 to 2007 in southwestern Ontario, Canada.

Premises type		Median shipment size (5^{th} & 95^{th} percentiles)	Shipment size (minima – maxima)
Source	Destination		
Sow	Nursery	203 (64–590)	9–1190
Sow	PUs	608 (21–1285)	1–1685
Nursery	Nursery	28 (1–218)	1–1580
Nursery	Finishing	243 (30–1943)	1–2355
Nursery	PUs	52 (9–318)	1–2930
Finishing	Finishing	15 (1–274)	1–2598
Finishing	PUs	82 (7–240)	1–1296

Table 5.4: Descriptive network metrics of swine shipments among three farm types estimated for the two-year period (2006–2007) in southwestern Ontario, Canada.

Network metrics	Overall	Sow	Nursery	Finishing
A. Network size				
i) Number of nodes (farms)	245	20	68	157
ii) Number of directed links	810	-	-	-
iii) Total number of shipments	5760	-	-	-
iv) Network size (all possible pair-wise links)	59780	-	-	-
B. Node level centrality measures - values reported are median (minimum and maximum range)				
i) Out-degree	1 (0–25)	6 (1–21)	8 (0–25)	0 (0–4)
ii) Normalized out-degree	0.41 (0.00–10.25)	2.46 (0.41–8.61)	3.28 (0.00–10.25)	0.00 (0.00–1.64)
iii) Frequency of off-farm shipments	1 (0–409)	203 (9–409)	16 (0–279)	0 (0–260)
iv) In-degree	3 (0–12)	-	3 (0–9)	3 (0–12)
v) Normalized median in-degree	1.23 (0.00–4.92)	-	1.03 (0.00–3.69)	1.23 (0.00–4.92)
vi) Frequency of onto-farm shipments	8 (0–363)	-	48 (0–215)	7 (0–363)
vii) Total degree	5 (1–29)	6 (1–21)	9 (1–29)	4 (1–13)
viii) Betweenness score	0 (0–106)	-	8 (0–106)	0 (0–52)
ix) Normalized betweenness score	0.00(0.00–0.18)	-	0.01 (0.00–0.18)	0.00 (0.00–0.09)
x) Eigenvector score	0.01 (0.00–0.23)	0.03 (0.00–0.18)	0.02 (0.00–0.23)	0.01 (0.00–0.14)
xi) Normalized Eigenvector score	1.72 (0.00–32.39)	3.94 (0.00–24.68)	2.74 (0.00–32.39)	1.13 (0.00–20.01)
C. Network level measures				
i) Density	0.014	-	-	-
ii) Out-degree centralisation index	8.9%	-	-	-
iii) In-degree centralisation index	3.6%	-	-	-
iv) Betweenness centralization index	0.17%	-	-	-
v) Diameter	5.0	-	-	-
vi) Median geodesic distance (mode)	2.0 (2.0)	-	-	-
vii) Clustering coefficient	0.09	-	-	-
viii) Fragmentation	0.96	-	-	-

Table 5.5: Clusters identified by hierarchical cluster analysis using weighted-average linkage method based on farm-level variables and measures of centrality of the swine shipments network analysis in southwestern Ontario, Canada. Values with superscript letter 'a' are reported in median and interquartile range.

Variable	Cluster#1 (n = 159)	Cluster#2 (n =62)	Cluster#3 (n = 10)	Cluster#4 n=13)	Cluster# 5 (n=1)
Farm size[a]	1,406 (250–2,700)	1,060 (360–2,760)	1,965 (1,000–4,000)	2,000(1,235– 2,540)	1,950
Shipment size[a]	39 (0–1,166)	0 (0–145)	346 (124–232)	467 (232–600)	2,352
Out-degree[a]	1 (0–15)	0 (0–3)	15 (12–21)	17 (13–25)	1
In-degree[a]	2 (0–6)	7 (4–12)	1 (0–3)	6 (4–9)	1
Betweenness[a]	0 (0–36)	0 (0–52)	4 (0–21)	58 (34–106)	0
Eigenvector[a]	0 (0–0.09)	0.01 (0– 0.14)	0.15 (0.10– 0.18)	0.16 (0.13–0.22)	0
Sow (%)	9.4	0	50.0	0	0
Nursery (%)	30.2	1.6	50.0	100	100
Finishing (%)	60.4	98.4	0	0	0

Table 5.6: Descriptive metrics of swine shipment network from farms to PUs (Network B) for the period 2006 to 2007 in southwestern Ontario, Canada.

Network metrics	Overall farms	Sow	Nursery	Finishing	PUs
A. Network size					
i) Number of nodes (premises)	300	12	54	143	91
ii) Number of links	740	-	-	-	-
iii) Total number of shipments	7,417	-	-	-	-
iv) Network size (all possible pair-wise links)	19,019	-	-	-	-
B. Node level centrality measures - values reported are median (minimum and maximum range)					
i) Degree	3 (1–24)	3 (1–4)	3 (1–11)	3 (1–24)	2 (1–144)
ii) Normalised degree	0.03 (0.01–0.26)	0.03 (0.01–0.04)	0.03 (0.01–0.12)	0.03 (0.01–0.26)	0.01 (0.01–0.29)
C. Network level measures					
i) Density (directed)	0.04	-	-	-	-
ii) Diameter	7.00	-	-	-	-
iii) Median geodesic distance	3.00	-	-	-	-

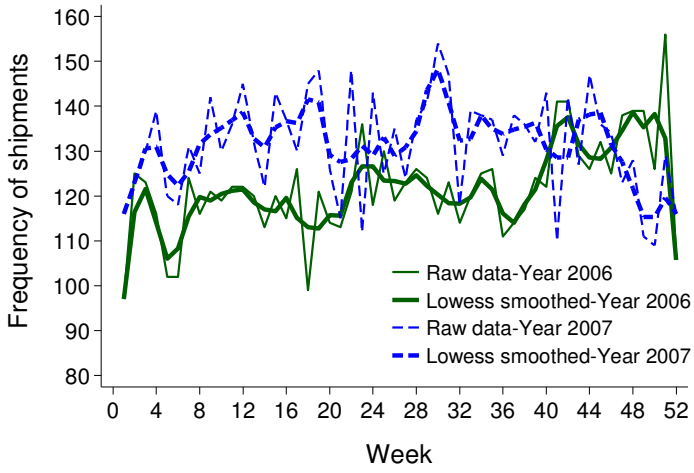

Figure 5.1: Frequency of weekly shipments of swine for 2006 and 2007 in southwestern Ontario, Canada. A lowess smoothing line was generated using locally weighted regression of frequency of shipments on weeks of each year with a bandwidth of 0.095.

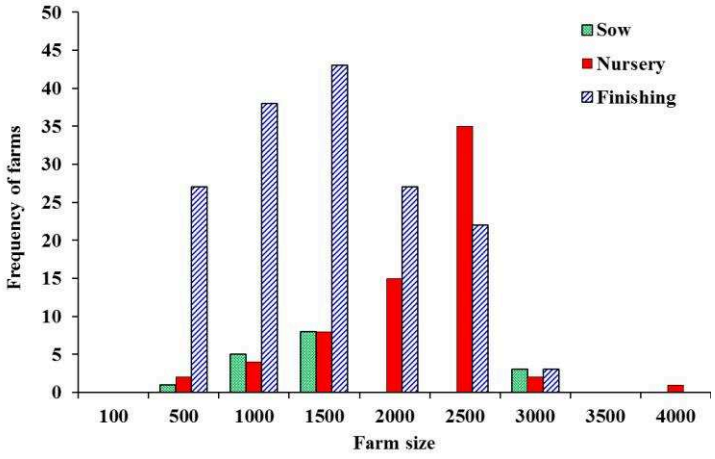

Figure 5.2: Distribution of the number of farms according to the total number of animals recorded in the database for the period 2006 to 2007 by farm type in southwestern Ontario, Canada.

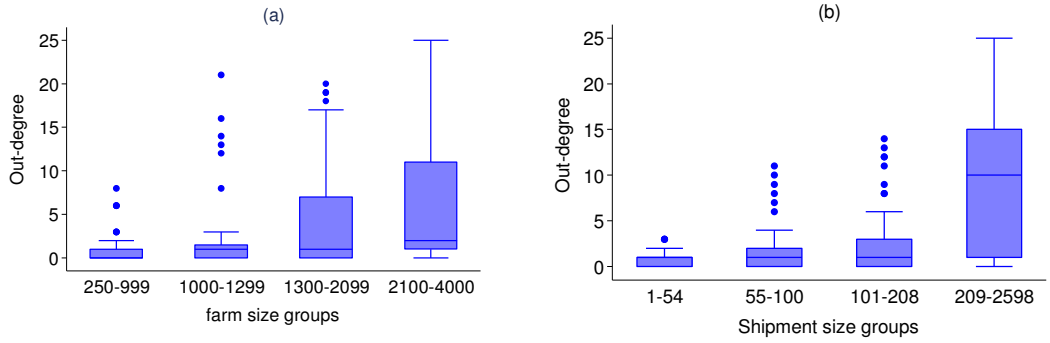

Figure 5.3: Out-degree distributions by: (a) farm size groups and (b) shipment size groups of a swine shipment network in southwestern Ontario, Canada.

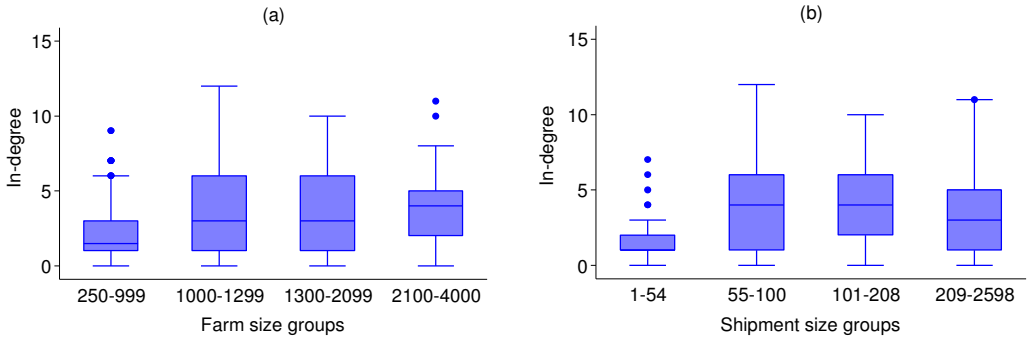

Figure 5.4: In-degree distributions by: (a) farm size groups and (b) shipment size groups of a swine shipment network in southwestern Ontario, Canada.

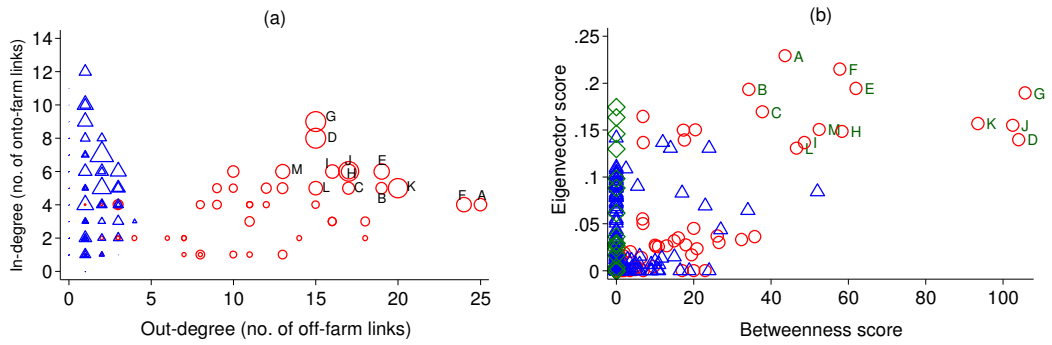

Figure 5.5: Scatter plot distributions of: (a) in-degree versus out-degree of nursery (red circle) and finishing (blue triangle) farms where size of marker is proportional to the betweenness centrality scores (sow farms are not shown as they have zero in-degree and betweenness score); and (b) Eigenvector versus betweenness scores of sow (green diamond), nursery (red circle) and finishing (blue triangle) farms involved in the swine shipment network in southwestern Ontario. Labeled farms belonged to cluster 4 groups that may play a central role in terms of vulnerability to disease introduction and spread to other farms as they have high key network measures; particularly farms K, J, D, and G with highest betweenness centrality measure.

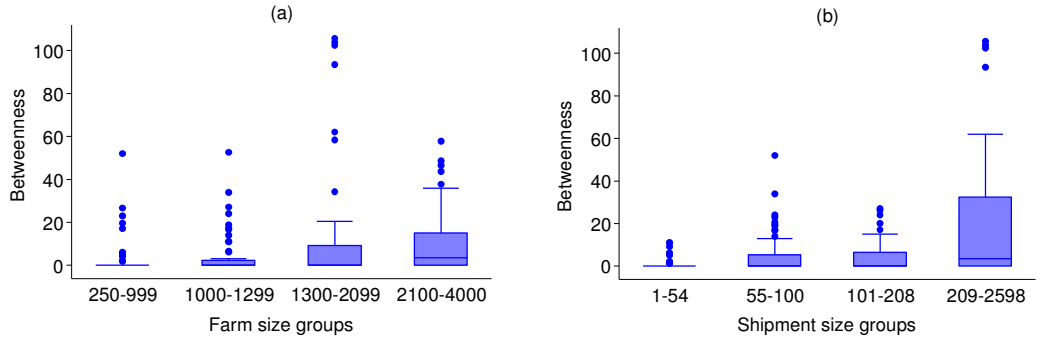

Figure 5.6: Betweenness centrality score distributions by: (a) farm size groups and (b) shipment size groups of a swine shipment network in southwestern Ontario, Canada.

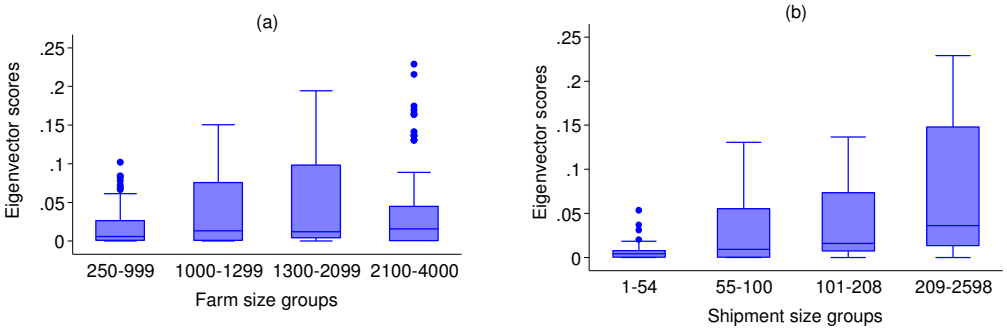

Figure 5.7: Eigenvector centrality distributions by: (a) farm size groups and (b) shipment size groups of a swine shipment network in southwestern Ontario, Canada.

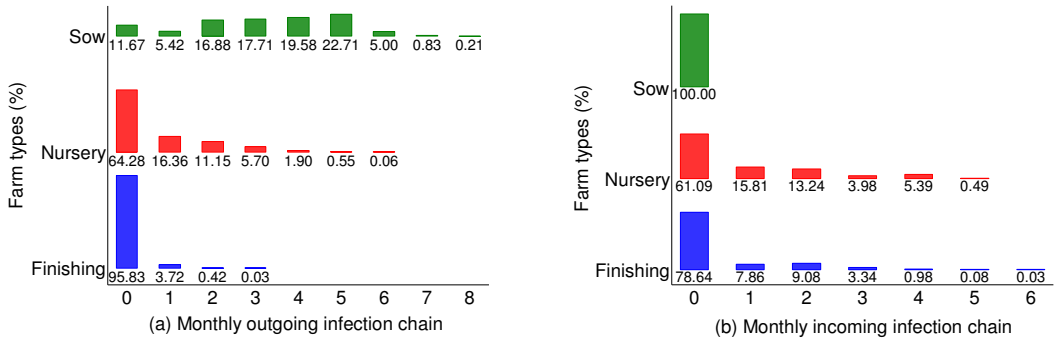

Figure 5.8: Percentage of farms with a given number of monthly: (a) outgoing infection chain and (b) incoming infection chain values for each of the three farm types described in the network analysis of swine shipments in southwestern, Ontario, Canada.

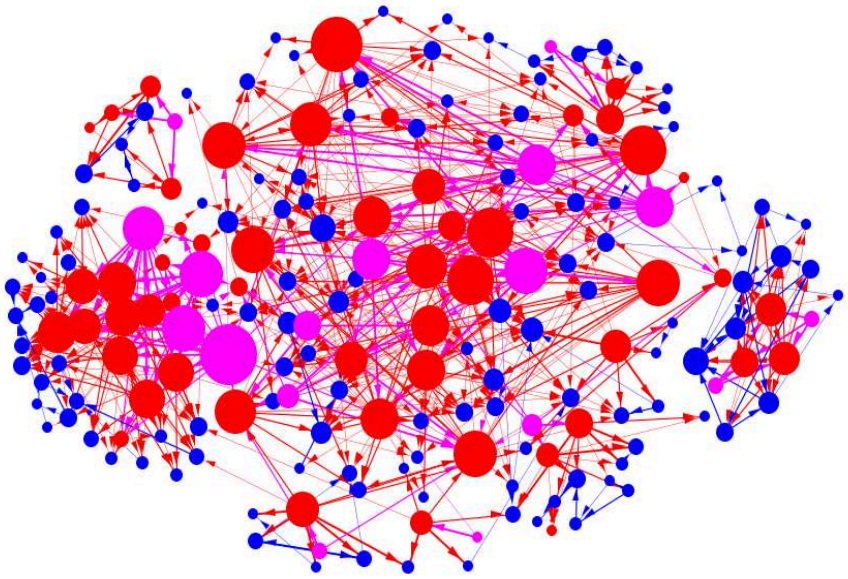

Figure 5.9: Network of swine shipment among three farm types in southwestern Ontario, Canada. Node sizes and width of links are proportional to the total degree and three categories of frequency of shipments (1, 2–10 and 11–258). Key: sow herd (pink); nursery (red); finishing (blue).

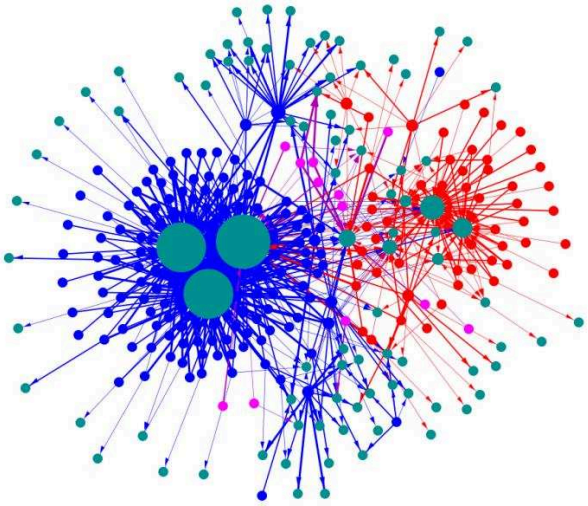

Figure 5.10: Two-mode network of swine shipment from farms to processing units in southwestern Ontario, Canada. Node sizes and width of links are proportional to the total degree and three categories of frequency of shipments (1, 2–10 and 11–117). Key: sow herd (pink); nursery (red); finishing (blue), processing units (green).

Chapter 6

Assessing the Effects of Network Structures on the Spread and Control of Diseases using Agent-based Modeling: A Case of Influenza in Swine Populations

6.1 Abstract

Recently network-based modeling studies have demonstrated that the spread and control of infectious diseases in human and animal populations are significantly affected by the structure of contact networks. We evaluated whether the generic findings of these studies are valid in a setting of a specialized multi-site all-in all-out swine production system. We constructed an agent-based model comparing three theoretical networks: random (RN), scale-free (SFN) or small-world (SWN). We used the pandemic influenza H1N1 2009 virus as a case study in a study population of 500 swine farms, equivalent to the population of a county in Ontario, Canada. The results indicated a faster spread, with higher peak prevalence and larger epidemic size in the SWN models compared with the SFN and the RN models, contrary to the findings in other species of animal and human populations. The spread of influenza tended to be faster with higher peak prevalence and higher overall epidemic size in the SFN compared with the RN models consistent with the previous studies. However, these differences were not statistically significant. A strategy that quarantined all farms with a number of links $\geq 75^{th}$ percentile distribution had the maximum benefit in containing the disease outbreaks (with relatively lower peak prevalence and overall size of the outbreaks) compared with a strategy targeting farms with a number of links $\geq 95^{th}$ percentile distribution. In conclusion, future infectious disease modeling work in similar swine production system should consider incorporating appropriate network structures to improve the validity of the model's predictions, and to support better policy decisions.

Keyword: Influenza, H1N1 virus, swine, pigs, agent-based models, network modeling

6.2 Introduction

Simulation models are being used to predict the extent of spread, to evaluate intervention strategies, and to both develop and assess contingency plans for infectious diseases in human (Lipsitch et al., 2003, Lloyd-Smith et al., 2003, Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Halloran et al., 2008, Gojovic et al., 2009, Tuite et al., 2010) and animal populations (Morris et al., 2001, Kao, 2002, Garner and Beckett, 2005, Shirley and Rushton, 2005a, Kiss et al., 2006b, Sharkey et al., 2008, Dürr et al., 2013). While the majority of early disease spread models used aggregate or compartmental models, an increasing trend towards the use of more complex stochastic agent-based models has been reported (Keeling and Eames, 2005, Lloyd-Smith et al., 2009, Woolhouse, 2011, Dorjee et al., 2013a). In an agent-based model (ABM), each 'agent' is represented explicitly and the model tracks its infection status or other attribute over time (for this reason these are also referred to as "individual-based" models). This is in contrast to the aggregate or compartmental model where individuals are followed collectively as a group over time. Agent-based models offer the advantages of greater flexibility to incorporate individual-level heterogeneities such as age, sex, risk of susceptibility to an infection, historical health information (for example vaccination status, waning immunity, in-utero exposure to infectious agent, etc.), as well as spatial location. In addition, contact tracing of exposed individuals to an

infection and targeted intervention measures can be more easily implemented in this type of model.

Recently, a growing number of modeling studies have extended the agent-based approach further by explicitly incorporating either empirical or theoretical contact networks of disease spread and intervention measures, in human (Moore and Newman, 2000, Eames and Keeling, 2002, Riley et al., 2003, Eubank et al., 2004, Hufnagel et al., 2004, Shirley and Rushton, 2005b, Rahmandad and Sterman, 2008, Rahmandad et al., 2011) and animal populations (Green et al., 2006, Kao et al., 2006, Kiss et al., 2006b, Kiss et al., 2006a, Kiss et al., 2008, Sharkey et al., 2008, Vernon and Keeling, 2009, Dürr et al., 2013, Fournié et al., 2013). In a real-world situation a given individual has contact with only a limited number of other individuals in a population, and this may vary significantly from one individual to another. Frequency and patterns of linkages between individuals result in the formation of networks with different contact topologies. Many real-world structures of social, technological and biological interactions are characterized by scale-free network (SFN) and/or small-world network (SWN) topologies (Newman, 2002, Newman, 2003, Keeling and Eames, 2005, Danon et al., 2012), including those associated with livestock movements between farms (Christley and French, 2003, Bigras-Poulin et al., 2007, Clauset et al., 2009, Dubé et al., 2009, Martinez-Lopez et al., 2009, Lockhart et al., 2010). In a SFN, a large number of nodes/vertices (representing a person, farm or other entities of interest) have few links, while a limited number of nodes have a relatively large number of links, following a

power-law distribution (Barabasi and Albert, 1999, Barabasi and Bonabeau, 2003). Such networks are hypothesized to evolve through preferential attachment of new nodes to the existing nodes that are highly connected. Small-world networks are characterized by clusters of nodes that are connected to each other through a few long-range links. Therefore, a SWN will have a relatively high clustering coefficient and shorter geodesic distance than a random network (RN) of equivalent size (Newman, 2003, Shirley and Rushton, 2005b, Dubé et al., 2009). Although many complex empirical networks are possible in the real-world, the effects of network topologies on the spread of diseases and on the effectiveness of intervention strategies have been studied using four theoretical networks. These are RN, ring-lattice, SWN and SFN (Keeling and Eames, 2005, Shirley and Rushton, 2005b, Rahmandad and Sterman, 2008). These studies have shown that the speed and extent of disease spread, as well as the effectiveness of control strategies, are significantly affected by network topology. This being the case, even a complex and stochastic agent-based model which assumes random-mixing rather than adopting a suitable contact network structure, will be unrealistic in many situations. Therefore, it is recommended that an appropriate network structure be explicitly incorporated to increase the validity of such models (Keeling and Eames, 2005).

Currently, network modeling studies that have assessed the effects of network structures (theoretical and empirical) on the spread and control of diseases in livestock have mostly focused on a limited set diseases; including foot-and-mouth disease (FMD) (Green et al., 2006, Kao et al., 2006, Kiss et al., 2006b, Kiss et al., 2006a, Kiss et al.,

2008, Vernon and Keeling, 2009), highly pathogenic influenza viruses in poultry (Sharkey et al., 2008, Fournié et al., 2013) and classical swine fever (CSF) in Switzerland (Dürr et al., 2013). Live swine shipments among farms/premises have been shown to exhibit SFN and SWN topologies (Bigras-Poulin et al., 2007, Nöremark et al., 2011, Rautureau et al., 2012, Buttner et al., 2013, Dorjee et al., 2013b). To our knowledge, no study has yet evaluated the effects of making different network topology assumptions on the spread and control of influenza in swine populations. Therefore, the main objective of this study was to evaluate the effects of network topology and heterogeneities in contacts among different farm types on the spread and control of influenza. Specifically, this study investigated the effects of three common network topologies (RN, SFN and SWN) on the speed and extent of influenza spread among farms, in conjunction with various control strategies, assuming a multi-site all-in all-out (AIAO) production system. For this study, the pandemic influenza A H1N1 2009 (pH1N1) virus has been used as the case example. The results of this study should also provide guidance as to how important it is to incorporate a complex network structures into future disease spread modeling research which targets similar production systems. Furthermore, this modeling exercise could be adapted and applied to other infectious diseases of swine, such as FMD, porcine respiratory and reproductive syndrome (PRRS), or CSF.

6.3 Materials and Methods

6.3.1 Study populations

A synthetic study population of 500 swine farms, approximately equal to the number of swine farms of Perth County (a county with the highest swine farm density) in Ontario, Canada was generated. A total of 488 swine farms with 664,508 pigs were recorded in the 2006 census year for this county (Statistics Canada, 2007). The majority of the swine farms in Ontario consist of specialized multi-site production systems; such as breeder, farrow-to-wean, farrow-to-finish, nursery, wean-to-finish or finishing farms. These farms are operated either as continuous-flow or AIAO systems of management. Furthermore, AIAO production systems are operated as either AIAO by barn or by site (McEwan and Marchand, 2007, Varela et al., 2007, Owsley et al., 2013). For simplicity, swine premises were categorized into three types, namely sow (50), nursery (150) and finishing (300) farms, and AIAO by site was assumed for nursery and finishing farms, but not for sow farms. In the AIAO by site production system, all barns are filled or emptied of pigs at the same time. Barns are then cleaned, disinfected and kept empty for 7–14 days (referred to as 'down-time') (Scheidt et al., 1995, Owsley et al., 2013). The number of farms assigned to each category was based on the approximate proportion of the three farm types (8% of sow, 28% of nursery, and 64% of finishing farms) observed in the swine population data used in a previous network analysis study (Dorjee et al., 2013b). Sow farms consisted of breeder farms, farrow-to-wean or farrow-to-finish operations, nursery farms housed pigs of 3-10 weeks of age, and finishing farms housed

pigs of approximately 11 weeks to market age. It was assumed that live pigs were shipped in a directed flow from sow to sow, sow to nursery, sow to finishing, nursery to finishing, and finishing to sow (gilt replacement) farms. Accordingly, the influenza spread among farms was modeled by direct contact through the shipment of live pigs. The potential spread by indirect contact, through the movement of people, contaminated fomites, etc. was ignored due to lack of information and for simplicity of model construction.

6.3.2 Structure of models

The effect of three commonly reported network topologies, namely RN, SFN and SWN on the spread and control of influenza among swine farms were compared using an agent-based network models (ABNM). A simple deterministic system dynamic or aggregate compartmental model (SDM), that treated farms as a single type, was also constructed for comparison with the ABNMs. A basic unit of simulation was implemented at the farm level. All units within each category of farm type were considered identical in terms of size, breeds, management practices, using the approach similar to that adopted by Vernon and Keeling (2009). Therefore, any effects of these variables on the transmission dynamics of influenza could not be assessed. Although a crude assumption, this approach allows for an evaluation of the effect of network topologies in isolation from other heterogeneities (Vernon and Keeling, 2009). All models were constructed and simulated in AnyLogic® version 6.9.0 (XJ Technologies, Russia).

6.3.2.1 System dynamic model (SDM)

A susceptible-exposed-infectious-recovered (SEIR) structure was used for the SDM. Simulations using the SDM were started by seeding the infection in a single farm (exposed state). In this model, farms are grouped into one of the mutually exclusive influenza disease states at each time-step (per day basis) of the simulation. Each exposed or infectious farm infects susceptible farms based on the contact rate and probability of transmission of infection per contact. Groups of farms transit from one disease state or compartment to another based on the rate defined by the nonlinear differential equations described below (Rahmandad and Sterman, 2008, Vynnycky and White, 2010):

equation 1:

$$\frac{dS}{dt} = -f$$
$$\frac{dE}{dt} = f - e$$
$$\frac{dI}{dt} = e - r$$
$$\frac{dR}{dt} = r$$

Where:

- S, E, I, R are the number of individuals (e.g. farms) in the susceptible, exposed, infectious and recovered compartments per unit time and S+E+I+R=N (total number of farms);
- f = flow rate from a susceptible to exposed compartment per unit time = ((contact frequency between exposed and susceptible farms * probability of

transmission per contact *E) + (contact frequency between infectious and susceptible farms * probability of transmission per contact * I)) * (S/N);

- e = flow rate from exposed to infectious compartment per unit time = 1/average duration of exposed period * E;
- r = flow rate from infectious to recovered compartment per unit time = 1/average duration of infectious period * I.

The major assumptions of the SDM were: all farms were totally susceptible to the influenza virus; individual farms within each compartment were homogeneous and perfectly mixed (i.e. same contact probability among farms); probabilities of farms moving from the exposed to infectious, and to the recovered compartments were independent of how long a farm had been in the exposed or infectious states; there was no addition or loss of farms during the simulated period (closed population). Furthermore, exposed farms were assumed infectious as the shipment of live pigs from exposed farms (farms with infected animals in the incubation stage) would result in infection of susceptible farms.

6.3.2.2 Agent-based network model (ABNM)

The same SEIR model structure was assumed for sow farms, whereas SEIRS was used for nursery and finishing farms for all the ABNMs (Figure 6.1). This was because the nursery and finishing farms were no longer susceptible to infection during the down-time of 14 days in the AIAO system of management (as no pigs were housed on a farm).

The nursery and finishing farms returned to a susceptible state once they were restocked with a new batch of pigs at the end of each period of down-time.

Although the model structure of the SDM and ABNMs are similar, the disease states of each individual farm were explicitly represented in the ABNMs. That is each individual farm $j \in (1,\ldots..N)$ existed in one of the four mutually exclusive disease states at any given time step (i.e. day) of the simulation. Disease state transitions f (j), e (j), and r (j) of each farm represent one instant of infection, transition from the exposed to infectious states (e = emergent), or from the infectious to recovered states (r = recovery), respectively, and zero otherwise (that is it remained in the same disease state). In the case of nursery and finishing farms, s (j) represents one moment of transition from a recovered to a susceptible state, occurring at the end of recovered period (equivalent to the duration of down-time period). In the agent-based approach, the model keeps track of each individual farm and sums up the individual transitions to estimate the total population in each of the disease states at the end of each time-step of the simulation (Rahmandad and Sterman, 2008, Vynnycky and White, 2010). Agent-based models relax the assumptions of homogeneity and perfect mixing and capture individual heterogeneities in terms of number of links and other attributes associated with the disease transmission process. At each iteration, a sow farm was initially infected using one of the two approaches: (i) a premises with a maximum number of links in the networks being evaluated; or (ii) by random selection. At each iteration, the links were assigned randomly among farms depending on the network structure described below.

The probability of a farm being infected depended on the disease states of all farm linked to it. Every day, every exposed or infectious farms contacted other farms connected to it randomly with certain contact frequency (as defined in Table 6.1), and with a probability equal to a transmission probability sent the message “Infect” to these farms. If a farm receiving the message “Infect” was a susceptible farm then it got infected and transited to the exposed state. Once exposed/infected every farm transited from exposed to infectious state (e = emergent) based on the rate 1/exposed duration, and then from infectious to recovered state (r = recovery) based on the rate 1/infectious duration. Subsequently, nursery and finishing farms transited from a recovered or from quarantined to susceptible state at the end of ‘down-time’. In the case of sow farms that were quarantined, they transited to susceptible state at the completion of one-month quarantine duration. All of these transitions were modeled by stochastic processes.

6.3.2.3 Network topology

The theoretical RN, SFN and SWN topologies used in this study were constructed using random (Erdös and Rényi, 1960), small-world (Watts and Strogatz, 1998), scale-free (Barabasi and Albert, 1999) algorithms that are inbuilt in AnyLogic®. The SFN was constructed based on the preferential attachment process where the probabilities of new farms linking to the existing farms were proportional to the number of links the existing farms already have. The network construction started by M_0 initial number of farms connected to each other. Then at every time step a new farm was added to the network

so that a new farm was connected to M ($\leq M_0$) already existing farms with a probability that was proportional to the number of links that the existing farms already have. This process was repeated until a network size of 500 farms was reached. AnyLogic® requires that only a value of M be specified, and we used $M_0 = M = k = 4$, where k was the average number of links per farm (XJ Technologies, 2007, Rahmandad and Sterman, 2008). An average of four links per farm (k = 4) was assumed based on the result of the previous network analysis study (Dorjee et al., 2013b). The distribution of links among farms in SFN follows a power-law function, where the probability that a farm has k links (probability (k)) $\propto k^{-\gamma}$, where γ is the scaling exponent.

Three types of SWNs were constructed from a ring-lattice network by re-connecting a proportion of the links to long-range links according to the following probabilities: 0.05 (SWN-0.05), 0.10 (SWN-0.10) and 0.30 (SWN-0.30). A probability of 0.05 with average of 4 links/farm among 500 farms resulted in a clustering coefficient of approximately 0.42 and an average path length of 10, which are higher than those observed in a previous study (Dorjee et al., 2013b); while a probability of 0.30 resulted in a clustering coefficient of 0.22 and an average path length of 6, values that are approximately similar to those in the study noted above. The average path length did not decrease below 5 despite increasing the probability of long-range links to 0.50 to 0.60, while the clustering coefficient decreased to 0.059 for the 0.50 probability of a long-range links. Therefore, the impact of SWN was assessed at three levels noted above in terms of long-range links in the sensitivity analysis.

The default features regarding network construction in AnyLogic® establish links among all possible pairs of farm types. Our study required no connection between nursery to nursery or between finishing to finishing farms. As such, customized Java code was built into AnyLogic® to disconnect the links between nursery-to-nursery and finishing-to-finishing farms, these disconnected links were then re-wired among pairs of farms randomly in consistent with the contact structures outlined above. In addition, directional links were used so the infection was transmitted between pairs of farms in one direction only. This was achieved by the way in which the 'infection message' was passed and received between by each pair of linked farms. For example, a sow farm could receive the 'infection message' from other sow or finishing farms but not from any of the nursery farms.

6.3.3 Quarantine strategies

The behavior of each model was investigated in response to three quarantine strategies: (i) general quarantine implemented through a reduction in the contact rate between all farms (irrespective of their disease states in all the three types of network models); (ii) random quarantine of individual farms (irrespective of their disease states); and (iii) targeted quarantine of highly connected farms (irrespective of their disease states). The latter two strategies were assessed only in the SFN models. The general quarantine measure was modeled as a reduction in the contact frequency (Cjs) between infectious farms, , $j \epsilon \{E, I\}$ and susceptible farms, $s \epsilon \{S\}$, where the contact frequency decreased linearly from the initial value Cjs to the minimum rates achieved under contact

reduction ($C^q js$), as the cumulative number of cases increased as defined by the equation below (Rahmandad and Sterman, 2008):

$$Cs = (1-q)Cjs + qC^q js \quad \textit{...equation 2}$$

$$q = \text{Min}[1, \text{Max}(0, (P-P_0)/(P_q - P_0))] \quad \text{...equation 3}$$

Where the proportion of contact reduction (q) increased linearly from zero to one over time as the number of cases (cumulative prevalence (P) = infectious + recovered) increased from a threshold (P_0) to the level at which a maximum reduction was achieved (Pq). We used $P_0 = 10$ farms and $P_q = 50$ farms. As the quarantine measure cannot be implemented perfectly, the minimum contact frequency achieved ($C^q js$) was set to 0.05Cjs (that is the reduction of 95% from the normal contact rates). The contact reduction for general quarantine strategy was assumed to have been achieved through policy responses (mandatory isolation and movement restriction) as well as voluntary isolation (that is farms on receiving the disease outbreak notification voluntarily stopped receiving and sending animal shipments to other farms).

The random and targeted quarantine strategies were evaluated only in SFN models because it was not logical to assess the targeted quarantine strategy in RN and SWN models as all farms would have similar number of links. In a random quarantine strategy, two farms from each production type, irrespective of their disease states were quarantined randomly on a daily basis. Although a random quarantine strategy is rarely implemented in practice (perhaps only in cases when authorities do not have any knowledge in the underlying contact patterns), it was investigated to provide a baseline

'worst-case scenario' to compare it with the effect of the targeted quarantine strategy. Two scenarios of targeted quarantine strategies were evaluated; targeting only those farms with number of links: (i) $\geq 75^{th}$ percentile, or (ii) $\geq 95^{th}$ percentiles of the overall link distribution. Transition of farms either from the susceptible, exposed or infectious state to quarantined state (Figure 6.1) were triggered by a 'message' when a threshold of $P_0 = 10$ farms was reached. Farms remained in the quarantined state permanently for the duration of the simulation.

6.3.4 Model parameters

The parameters used for the SDMs and ABNMs are presented in Table 6.1, and were derived from the literature or otherwise assumed. No information on the exposed or infectious duration of influenza infections at the farm level was available. Therefore, it was assumed that the farm-level duration of the exposed state was equal to individual pig level value. In effect this means that farms were considered exposed from the time a single pig became infected up until the time when the first pig becomes infectious. The farm-level duration of infectious state varies with a farm size. Accordingly, infectious duration of sow farms was generated from an individual-level parameters using the WithinHerd software version 0.9.5 (Reeves et al., 2013). This is a stochastic modeling framework that simulates the within-unit disease spread and generates herd-level durations of disease states. A farm size distribution of BetaPert(500, 1200, 3000), equivalent to that observed in a previous study (Dorjee et al., 2013b) was used for this exercise. Infectious periods of 32 and 120 days were assumed for nursery and finishing

farms, respectively, after subtracting the exposure time. These values represent the duration that pigs remained in nursery and finishing farms. No information on the probability of influenza transmission per contact between swine farms was available. Therefore the transmission probability (infectivity) of 0.1 and 0.9 was assumed for exposed and infectious farms, respectively.

6.3.5 Statistical analyses

A total of 28 scenarios were evaluated. The outcomes of SDM and five ABNMs (RN, SFN, and three SWN models with different probabilities of long-range links) for the spread and general quarantine strategy were evaluated (2 SDMs + 5 ABNMs x 2 = 12 scenarios). In addition, five ABNMs were evaluated under the two initial infection settings (5 x 2 = 10 scenarios). Furthermore, three quarantine strategies (of random and two targeted quarantine options) using SFN models under the two settings of the infection seeding were compared (3 x 2 = 6 scenarios). A total of 500 iterations were simulated to capture the stochastic variability of each scenario. Models outcomes are reported in terms of parameters relevant from an epidemiological or regulatory perspective, such as stochastic 'die-out' fraction (a fraction of simulations that do not lead to an outbreak; defined as no farms infected), time-to-peak epidemic day (day on which the highest number of infectious farms was observed), peak prevalence (highest number of infectious farms observed at the peak epidemic day), overall epidemic size (total number of farms infected), and duration of outbreak (time-to-end of outbreak, defined as the time until no exposed and infectious farms were present, or a cut-off

value of 365 days in cases when it extended beyond that day). Descriptive statistics were calculated in terms of the 5th, 50th and 95th percentiles. Differences in the outputs between different models were compared using Kruskal-Wallis test with Bonferroni post hoc test at 5% significance level.

6.4 Results

6.4.1 Stochastic 'die-outs' fraction

The stochastic 'die-out' fraction were higher in the settings where infection was seeded in a sow farm randomly and when the general quarantine strategy was implemented (Figure 6.2). However, the stochastic 'die-out' fractions were similar among different network-based models within the same type of infection seeding and with or without the implementation of the general quarantine strategy, except in scenarios where the infection was seeded in a maximally connected sow farms.

6.4.2 Epidemic size and duration

The results from 22 simulated scenarios (the spread and the general quarantine strategy scenarios) are summarized in Table 6.2. For the models assessing transmission dynamics (section A - influenza spread models without imposing any quarantine measures), the medians of time-to-peak epidemic day were relatively shorter in SWN-0.05 and SWN-0.10 compared with other models in both the settings of infection seeding. In addition, this measure was similar for the RN, SFN and SWN-0.30 models, and comparable to that predicted by the SDM model, under the setting when infection was seeded randomly. However, the magnitude of this difference was larger between RN, SFN and

SWN-0.30 when the infection was seeded in a maximally connected sow farm (index case). The predicted peak prevalence and the overall epidemic size when using SDM were both significantly higher than was the case for any of the ABNMs. The outbreak duration of the SDM subsided in 296 days, whereas it typically continued beyond the one-year simulation period in all the ABNMs. The 5th percentiles of the overall duration were relatively shorter for RN, SFN and SWN-0.05 compared with SWN-0.10 or SWN-0.30 models (results not shown). Given the assumptions of the models, the results indicated that the influenza spread among farms was faster with higher peak prevalence and the overall epidemic size in the SWNs than in RN or SFN models, under both the settings of the infection seeding. Both the medians of peak prevalence and the overall size of the epidemics of the SWNs models were approximately twice the values observed from either RN or SFN models under the setting of random seeding of the infection (Table 6.2 A.1 and Figure 6.3). However, these differences were of lesser magnitude for the setting where infection was seeded in a maximally connected sow farm. No significant differences were observed in all the outcome metrics between RN and SFN in both the settings of infection seeding. However, the influenza spread trended to be relatively faster with higher peak prevalence and overall epidemic size, in the SFN than RN models.

The median time-to-peak epidemic day was longer by approximately 2–4 weeks in both the maximally seeded RN and SFN than randomly seeded same models. The medians of peak prevalence and the sizes of epidemics of RN and SFN models with the

infection seeded in a maximally connected sow farm was 1.5 to two times higher than that of the same models where the infection was seeded into a single randomly selected sow farm (Table 6.2 A.2). However, no significant difference was observed between the two seeding approaches across all types of SWNs.

6.4.3 Control strategies

Amongst the models assessing the effect of the general quarantine strategy (Table 6.2, section B), the outcomes related to the SDM were similar to those of the RN and SFN models, except that the time taken to the peak epidemic day and the duration of the outbreak were shorter in the case of the SDM. The similar trend was observed amongst the different ABNMs in the peak prevalence and the overall epidemic size as in the disease spread scenarios, except the time-to-peak epidemic days were similar among all the models.

The results indicated that the general quarantine strategy implemented as a reduction in the contact rate among farms was not effective at the level specified in the models as peak prevalence, the overall epidemic size and duration of outbreaks were similar to those scenarios without the implementation of the quarantine measure (Table 6.2 B). However, imposing general quarantine measure significantly delayed the time to the peak epidemic day by 14–34 days for RN, SFN and SWN-0.30. These differences were relatively smaller in the case of SWN-0.05 and SWN-0.10. In contrast, the quarantine strategies that quarantined farms randomly or highly connected farms selectively (triggered when ≥10 farms were infected) were effective in containing the spread of the

influenza. Furthermore, quarantining all farms with a number of links ≥75th percentiles of the overall link distribution was the most effective (Table 6.3, Figure 6.4 (b)). The time taken to reach the peak epidemic day was shorter and the overall epidemic size was lower (by half the length and number) in the case of quarantine strategy targeting farms with number of links ≥75th percentile of the overall link distribution than the strategy that targeted farms with links ≥95th percentile of the link distribution or simply did so randomly. In addition, under this quarantine strategy the approximately twice difference in the number of units infected in a maximally seeded SFN model compared with randomly seeded SFN models observed was no longer true. All the outcome measures were similar between the two types of seeding of infection across the three models assessing alternative targeted quarantine strategies. The number of farms quarantined was also relatively more in the random strategy than the targeted quarantine strategies (Table 6.3 and Figure 6.5).

6.5 Discussion

In this study we evaluated the effects of network topologies on the spread and control strategies for pH1N1 among swine farms using ABNMs. These models explicitly incorporated realistic contact structures (contacts between sow farms, sow to nursery farms, etc.) and different contact rates between pairs of farm types. The results from this study can be used to gauge the value of explicitly incorporating network structure into the models of this type. Alternatively, they help inform the question as to whether

relatively simpler ABMs with random mixing, are adequate for modeling influenza and other infectious diseases in the similar swine production system.

The results indicated that a simple SDM overestimated the peak prevalence and the overall epidemic size, while underestimating the duration of the outbreak when compared to all the ABNMs in the absence of quarantine measures. This is due to the homogenous and the perfect mixing assumption of SDM whereby the probability of infectious farms contacting susceptible farms is much greater (perfect mixing) in comparison to network-based models. This result suggests that SDM may not provide valid estimates of the key outcome metrics. However, the outcome measures from the SDM and RN or SFN models were similar when the general quarantine strategy was implemented. Strictly speaking it is not reasonable to compare model outputs from the SDM with the network-based models as the SDM considered all farms as a single type, whereas the contact rate, the duration of the infectious and recovered periods of different farm types were assumed different in the ABNMs. The crude comparison here provides a general understanding of the differences between an over simplified representation (SDM that treated all farms as homogenous) versus relatively realistic approaches to the modeling (RN, SFN and SWN models). Nevertheless these finding are consistent with a theoretical study that compared the outcome metrics of SDM and ABNMs (Rahmandad and Sterman, 2008). There are additional disadvantages of using SDMs, such as their inability to implement targeted quarantine measures or the difficulty in incorporating other agent-level heterogeneities which are often necessary within modeling studies

(Keeling and Eames, 2005, Shirley and Rushton, 2005a, Rahmandad and Sterman, 2008).

No significant differences in the epidemiologic metrics evaluated were observed between the RN and SFN models that assessed the spread of the virus without quarantine or under a general quarantine strategy. This would suggest a relatively simpler agent-based approach assuming random mixing can be used for modeling influenza spread in a similar swine production system, given the assumptions outlined in these models. This is because the RN model can be treated as the equivalent of an agent-based model with a random mixing (Keeling and Eames, 2005, Shirley and Rushton, 2005b, Rahmandad and Sterman, 2008). Although not significantly different, the speed of the influenza spread (time-to-peak epidemic day), peak prevalence, and overall epidemic size were all relatively higher in the SFN models than in the RN models, consistent with findings from other studies (Shirley and Rushton, 2005a, Kiss et al., 2006a, Rahmandad and Sterman, 2008). Network-based models may still provide the preferred option in cases where targeted quarantine strategies are being assessed, as discussed below. The lack of significant differences between the RN and SFN models observed in this study, as opposed to findings of other studies (Shirley and Rushton, 2005a, Kiss et al., 2006a, Rahmandad and Sterman, 2008) may be due to the relatively small network size combined with fewer farms having a limited number of contacts (links). A fewer average number of links per farm results in the scale-free networks of relatively narrower range of the distribution of links among agents (higher value of

scaling exponent of the power-law distribution), which in turn results in the similar estimates of the outcome metrics with that of RN models. This is apparent from the differences in results amongst the similar studies conducted by Rahmandad and Sterman (2008) that used an average of 10 links per agent in a network of 200 people, Shirley and Rushton (2005a) that used an average of 8 links per agent in a network size of 500 people, and Keeling and Eames (2005) that used an average of 4 links per agent (as was the case in this study) but with a network size of 10,000 individuals.

The significantly faster spread of influenza among farms with higher peak prevalence and the overall epidemic size, observed for the SWN models compared with the SFN or RN models indicates the strong effect of the long-range links on the spread of influenza, overriding even the effects of the scale-free network. These long-range links facilitate the rapid spread of the disease across wider regions of the network, resulting in higher overall number of farms infected (Keeling and Eames, 2005). The higher number of infection results because more susceptible farms are available at any given time for contact with the infectious farms. Even with only a few long-range links (5% of farms), significant changes in the metrics of influenza spread were evident, demonstrating the importance of this small-world effect. It is interesting to note the influenza spread was relatively slower with higher peak prevalence and the overall epidemic size in the SWN-0.30 model than SWN-0.05 or SWN-0.10. This is because the speed of spread of the influenza among the population was positively associated with the degree of local clustering of connections amongst the farms, as it was relatively higher in SWN-0.05

and SWN-0.10 models than with other models (RN, SFN, and SWN-0.30). Contrary to our findings, other studies have found that the speed of the disease spread tended to be faster, with higher peak prevalence, in SFN models than in SWN models (Keeling and Eames, 2005, Shirley and Rushton, 2005b, Rahmandad and Sterman, 2008). This might be due to the combination of small network size and the relatively low value for the average number of links per farm used in our study. It results in a relatively lower magnitude of the scale-free effect than the long-range effect of the small-world on the spread of influenza as explained above.

The higher peak prevalence and the overall epidemic sizes observed in the models when the infection was seeded in a maximally connected, rather than a randomly selected sow farm was due to the fact that an infection seeded in a maximally connected farm is more likely to generate a well-established outbreak in a population. This was also evident from the results relating to the stochastic 'die-out' fraction (Figure 6.2), particularly in the absence of quarantine strategy measure. It is important to investigate such scenarios in modeling research as highly connected farms are at greater risk of both receiving and spreading infection to other farms, and their early infection probably represents a worst case scenario in many disease outbreak situations. It also suggests that a general policy of requiring better routine biosecurity on all highly connected farms may be justified due to the negative impact they can have on the entire industry if they are the initial or an early case in a new disease outbreak.

It was evident that the targeted or random quarantine strategy had a significant beneficial effect than the general quarantine strategies. Given the assumptions in the models, the targeted strategy that quarantined all farms with a number of links $\geq 75^{th}$ percentile of the overall link distribution offered a maximum benefits than other strategies assessed in this study. However, a cost benefit trade-off in terms of disease control process versus impact on quarantining more number of harmless farms should be taken into consideration. For this knowledge to be practically useful it would be necessary to know the distribution of links among farms in advance for any disease outbreak situations, through contact network analysis. Even in the absence of contact tracing, quarantining highly connected farms may prove useful. However, targeted quarantine used in combination with the contact tracing may be a better and most effective strategy (Kiss et al., 2006a). Since the models investigated in this study were not spatially explicit we did not model local area or air-borne spread, nor did we model quarantine applied spatially relative to known infected farms (e.g. 3 km ring quarantine). These aspects may be studied in future work.

Some of the main limitations of this study include: a lack of information on the natural farm-level history of influenza infection (exposed, infectious, recovered duration) and farm-to-farm transmission probabilities to calibrate the models. Further sensitivity analysis needs to be conducted to evaluate whether these findings are consistent across all the plausible range of the transmission probabilities per contact and unit pairing. The default feature for SFN models in AnyLogic® does not allow for the

construction of customized SFNs based on average links per farm and a scaling exponent parameter, nor does it allow different sets of parameters to be specified between specific production types. It is not clear what value of the scaling exponent in the power-law distribution would be equivalent to the value of the M parameter used in this study. We also treated our links as binary and static; but previous studies found some important differences when treating the network as static as opposed to dynamic (Vernon and Keeling, 2009), and binary rather than weighted (Rahmandad and Sterman, 2008) in terms of the epidemic behavior of disease spread. In addition, we did not consider the indirect mechanisms of influenza transmission through the movement of people and other fomites which can also be important. Contact network structure as well as transmission dynamic and the persistence of the influenza virus could vary by production type and/or system of management (such as all-in-one versus multi-site production, continuous flow versus all-in-all-out operations, AIAO by barn or site, farm biosecurity levels, etc.). Therefore, future studies should investigate the findings presented here further in the context of alternative settings.

6.6 Conclusion

In conclusion, our study supported the findings of previous studies in that it demonstrated the presence of significant differences on the spread and control of infectious disease among different network structures in the specialized multi-site AIAO system of swine management. Contrary to previous findings, our study indicated that the effect of long-range connections among farms (the 'small-world' effect) had a larger

effect than topologies of RN or SFN on the speed of influenza spread and the overall outbreak size in the production system considered in this study. A targeted quarantine strategy involving all farms with ≥75th percentile distribution of links (upper inter-quartile range) provided the better benefit. Future modeling work on swine populations should attempt to incorporate appropriate network structures to improve the validity of the modeled outputs and ultimately to support better policy decisions. All of these findings are driven by the mathematics of the parameters used to describe any given network. Thus they will differ between networks with different characteristics (as in other studies). This in turn highlights the importance of understanding the characteristics of the network concern.

6.7 References

Barabasi, A. L. and R. Albert, 1999: Emergence of scaling in random networks. Science, 286, 509-512.

Barabasi, A. L. and E. Bonabeau, 2003: Scale-free networks. Sci. Am., 288, 60-69.

Bigras-Poulin, M., K. Barfod, S. Mortensen and M. Greiner, 2007: Relationship of trade patterns of the Danish swine industry animal movements network to potential disease spread. Prev. Vet. Med., 80, 143-165.

Brookes, S. M., A. Nunez, B. Choudhury, M. Matrosovich, S. C. Essen, D. Clifford, M. J. Slomka, G. Kuntz-Simon, F. Garcon, B. Nash, A. Hanna, P. M. Heegaard, S. Queguiner, C. Chiapponi, M. Bublot, J. M. Garcia, R. Gardner, E. Foni, W. Loeffen, L. Larsen, K. Van Reeth, J. Banks, R. M. Irvine and I. H. Brown, 2010: Replication, pathogenesis and transmission of pandemic (H1N1) 2009 virus in non-immune pigs. PLoS One, 5, e9068. doi:9010.1371/journal.pone.0009068.

Buttner, K., J. Krieter, A. Traulsen and I. Traulsen, 2013: Static network analysis of a pork supply chain in Northern Germany-Characterisation of the potential spread of infectious diseases via animal movements. Prev. Vet. Med., 110, 418-428.

Christley, R. M. and N. P. French, 2003: Small-world topology of UK racing: the potential for rapid spread of infectious agents. Equine Vet. J., 35, 586-589.

Clauset, A., C. Shalizi and M. Newman, 2009: Power-law distributions in empirical data. SIAM Review, 51, 661-703.

Danon, L., T. A. House, J. M. Read and M. J. Keeling, 2012: Social encounter networks: collective properties and disease transmission. J R Soc Interface, 9, 2826-2833.

Dorjee, S., Z. Poljak, C. W. Revie, J. Bridgland, B. McNab, E. Leger and J. Sanchez, 2013a: A review of simulation modelling approaches used for the spread of zoonotic influenza viruses in animal and human populations. Zoonoses Public Hlth, 60, 383-411.

Dorjee, S., C. W. Revie, Z. Poljak, W. B. McNab and J. Sanchez, 2013b: Network analysis of swine shipments in Ontario, Canada, to support disease spread modelling and risk-based disease management. Prev. Vet. Med., 112, 118-127.

Dubé, C., C. Ribble, D. Kelton and B. McNab, 2009: A review of network analysis terminology and its application to foot-and-mouth disease modelling and policy development. Transbound Emerg Dis, 56, 73-85.

Dürr, S., H. zu Dohna, E. Di Labio, T. E. Carpenter and M. G. Doherr, 2013: Evaluation of control and surveillance strategies for classical swine fever using a simulation model. Prev. Vet. Med., 108, 73-84.

Eames, K. T. D. and M. J. Keeling, 2002: Modeling dynamic and network heterogeneities in the spread of sexually transmitted diseases. Proc. Natl. Acad. Sci. U. S. A., 99, 13330-13335.

Erdös, P. and A. Rényi, 1960: The evolution of random graphs. Published. Math. Inst. Hung. Acad. Sci., 5, 17-61.

Eubank, S., H. Guclu, V. S. Anil Kumar, M. V. Marathe, A. Srinivasan, Z. Toroczkai and N. Wang, 2004: Modelling disease outbreaks in realistic urban social networks. Nature, 429, 180-184.

Ferguson, N. M., D. A. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn and D. S. Burke, 2005: Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature, 437, 209-214.

Ferguson, N. M., D. A. T. Cummings, C. Fraser, J. C. Cajka, P. C. Cooley and D. S. Burke, 2006: Strategies for mitigating an influenza pandemic. Nature, 442, 448-452.

Fournié, G., J. Guitian, S. Desvaux, V. C. Cuong, D. H. Dung, D. U. Pfeiffer, P. Mangtani and A. C. Ghani, 2013: Interventions for avian influenza A (H5N1) risk management in live bird market networks. Proc. Natl. Acad. Sci. U. S. A., 110, 9177-9182.

Garner, M. G. and S. D. Beckett, 2005: Modelling the spread of foot-and-mouth disease in Australia. Aust Vet J, 83, 758-766.

Germann, T. C., K. Kadau, I. M. Longini, Jr. and C. A. Macken, 2006: Mitigation strategies for pandemic influenza in the United States. Proc. Natl. Acad. Sci. U. S. A., 103, 5935-5940.

Gojovic, M. Z., B. Sander, D. Fisman, M. D. Krahn and C. T. Bauch, 2009: Modelling mitigation strategies for pandemic (H1N1) 2009. Can. Med. Assoc. J., 181, 673-680.

Green, D. M., I. Z. Kiss and R. R. Kao, 2006: Modelling the initial spread of foot-and-mouth disease through animal movements. Proc Biol Sci, 273, 2729-2735.

Halloran, M. E., N. M. Ferguson, S. Eubank, I. M. Longini, Jr., D. A. T. Cummings, B. Lewis, S. Xu, C. Fraser, A. Vullikanti, T. C. Germann, D. Wagener, R. Beckman, K. Kadau, C. Barrett, C. A. Macken, D. S. Burke and P. Cooley, 2008: Modeling targeted layered containment of an influenza pandemic in the United States. Proc. Natl. Acad. Sci. U. S. A., 105, 4639-4644.

Hufnagel, L., D. Brockmann and T. Geisel, 2004: Forecast and control of epidemics in a globalized world. Proc. Natl. Acad. Sci. U. S. A., 101, 15124-15129.

Kao, R. R., 2002: The role of mathematical modelling in the control of the 2001 FMD epidemic in the UK. Trends Microbiol., 10, 279-286.

Kao, R. R., L. Danon, D. M. Green and I. Z. Kiss, 2006: Demographic structure and pathogen dynamics on the network of livestock movements in Great Britain. Proc Biol Sci, 273, 1999-2007.

Keeling, M. and K. Eames, 2005: Networks and epidemic models. J R Soc Interface, 2, 295 - 307.

Kiss, I. Z., D. M. Green and R. R. Kao, 2006a: Infectious disease control using contact tracing in random and scale-free networks. J R Soc Interface, 3, 55-62.

Kiss, I. Z., D. M. Green and R. R. Kao, 2006b: The network of sheep movements within Great Britain: Network properties and their implications for infectious disease spread. J R Soc Interface, 3, 669-677.

Kiss, I. Z., D. M. Green and R. R. Kao, 2008: The effect of network mixing patterns on epidemic dynamics and the efficacy of disease contact tracing. J R Soc Interface, 5, 791-799.

Lange, E., D. Kalthoff, U. Blohm, J. P. Teifke, A. Breithaupt, C. Maresch, E. Starick, S. Fereidouni, B. Hoffmann, T. C. Mettenleiter, M. Beer and T. W. Vahlenkamp, 2009: Pathogenesis and transmission of the novel swine-origin influenza virus A/H1N1 after experimental infection of pigs. J. Gen. Virol., 90, 2119-2123.

Lipsitch, M., T. Cohen, B. Cooper, J. M. Robins, S. Ma, L. James, G. Gopalakrishna, S. K. Chew, C. C. Tan, M. H. Samore, D. Fisman and M. Murray, 2003: Transmission dynamics and control of severe acute respiratory syndrome. Science, 300, 1966-1970.

Lloyd-Smith, J. O., A. P. Galvani and W. M. Getz, 2003: Curtailing transmission of severe acute respiratory syndrome within a community and its hospital. Proc Biol Sci, 270, 1979-1989.

Lloyd-Smith, J. O., D. George, K. M. Pepin, V. E. Pitzer, J. R. C. Pulliam, A. P. Dobson, P. J. Hudson and B. T. Grenfell, 2009: Epidemic Dynamics at the Human-Animal Interface. Science, 326, 1362-1367.

Lockhart, C. Y., M. A. Stevenson, T. G. Rawdon, N. Gerber and N. P. French, 2010: Patterns of contact within the New Zealand poultry industry. Prev. Vet. Med., 95, 258-266.

Longini, I. M., A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D. A. T. Cummings and M. E. Halloran, 2005: Containing Pandemic Influenza at the Source. Science, 309, 1083-1087.

Martinez-Lopez, B., A. M. Perez and J. M. Sanchez-Vizcaino, 2009: Social network analysis. Review of general concepts and use in preventive veterinary medicine. Transbound Emerg Dis, 56, 109-120.

McEwan, K. and L. Marchand, 2007: Benchmarking the Ontario Pig Industry. University of Guelph, Ridgetown Campus, Guelph.

Moore, C. and M. E. J. Newman, 2000: Epidemics and percolation in small-world networks. Phys. Rev. E, 61, 5678-5682.

Morris, R. S., J. W. Wilesmith, M. W. Stern, R. L. Sanson and M. A. Stevenson, 2001: Predictive spatial modelling of alternative control strategies for the foot-and-mouth disease epidemic in Great Britain, 2001. Vet. Rec., 149, 137-144.

Newman, M., 2003: The structure and function of complex networks. SIAM Review, 45, 167-256.

Newman, M. E. J., 2002: Spread of epidemic disease on networks. Phys. Rev. E, 66, 016128.

Nöremark, M., N. Hakansson, S. S. Lewerin, A. Lindberg and A. Jonsson, 2011: Network analysis of cattle and pig movements in Sweden: measures relevant for disease control and risk based surveillance. Prev. Vet. Med., 99, 78-90.

Owsley, W. F. F., S. Rodning and J. Floyd, 2013: Scheduling all-in/all-out swine production. Alabama Cooperative Extension System (Alabama A&M University and Auburn University). Available at http://www.aces.edu/pubs/docs/A/ANR-0847/ANR-0847.pdf (accessed on 16 April 2013).

Rahmandad, H., K. Hu, R. J. Duintjer Tebbens and K. M. Thompson, 2011: Development of an individual-based model for polioviruses: implications of the selection of network type and outcome metrics. Epidemiol. Infect., 139, 836-848.

Rahmandad, H. and J. Sterman, 2008: Heterogeneity and Network Structure in the Dynamics of Diffusion: Comparing Agent-Based and Differential Equation Models. Manage. Sci., 54, 998–1014.

Rautureau, S., B. Dufour and B. Durand, 2012: Structural vulnerability of the French swine industry trade network to the spread of infectious diseases. Animal, 6, 1152-1162.

Reeves, A., M. Talbert, M. D. Salman and A. E. Hill, 2013: Development of a stochastic, individual-based modeling framework for within-herd transmission of highly infectious animal diseases. Prev. Vet. Med., (submitted).

Riley, S., C. Fraser, C. A. Donnelly, A. C. Ghani, L. J. Abu-Raddad, A. J. Hedley, G. M. Leung, L. M. Ho, T. H. Lam, T. Q. Thach, P. Chau, K. P. Chan, S. V. Lo, P. Y. Leung, T. Tsang, W. Ho, K. H. Lee, E. M. Lau, N. M. Ferguson and R. M. Anderson, 2003: Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. Science, 300, 1961-1966.

Scheidt, A. B., T. R. Cline and L. K. Clark, 1995: The effect of all-in-all-out growing-finishing on the health of pigs. J Swine Health Prod, 3, 202-205.

Sharkey, K. J., R. G. Bowers, K. L. Morgan, S. E. Robinson and R. M. Christley, 2008: Epidemiological consequences of an incursion of highly pathogenic H5N1 avian influenza into the British poultry flock. Proc Biol Sci, 275, 19-28.

Shirley, M. D. and S. P. Rushton, 2005a: Where diseases and networks collide: lessons to be learnt from a study of the 2001 foot-and-mouth disease epidemic. Epidemiol. Infect., 133, 1023-1032.

Shirley, M. D. F. and S. P. Rushton, 2005b: The impacts of network topology on disease spread. Ecol. Complexity, 2, 287-299.

Statistics Canada, 2007: Farm operators by farm type and province (2001 and 2006 Censuses of Agriculture) (Canada) (Summary Tables). Last updated May 16, 2007. Statistics Canada:http://www40.statcan.ca/l01/cst01/agrc22a.htm?sdi=farm%20operators (Accessed on 28 March 2010).

Torremorell, M., A. Juarez, E. Chavez, J. Yescas, J. M. Doporto and M. Gramer, 2009: Procedures to eliminate H3N2 swine influenza virus from a pig herd. Vet. Rec., 165, 74-77.

Tuite, A., D. N. Fisman, J. C. Kwong and A. Greer, 2010: Optimal pandemic influenza vaccine allocation strategies for the canadian population. PLoS Curr Influenza, RRN1144.

Varela, N. P., R. M. Friendship and C. E. Dewey, 2007: Prevalence of Campylobacter spp isolated from grower-finisher pigs in Ontario. Can. Vet. J., 48, 515-517.

Vernon, M. C. and M. J. Keeling, 2009: Representing the UK's cattle herd as static and dynamic networks. Proc Biol Sci, 276, 469-476.

Vincent, A. L., K. M. Lager, K. S. Faaberg, M. Harland, E. L. Zanella, J. R. Ciacci-Zanella, M. E. Kehrli, Jr., B. H. Janke and A. Klimov, 2010: Experimental inoculation of pigs with pandemic H1N1 2009 virus and HI cross-reactivity with contemporary swine influenza virus antisera. Influenza Other Respi Viruses, 4, 53-60.

Vynnycky, E. and R. White, 2010: An introduction to infectious disease modelling. Oxford University Press, Oxford, UK.

Watts, D. J. and S. H. Strogatz, 1998: Collective dynamics of 'small-world' networks. Nature, 393, 440-442.

Woolhouse, M., 2011: How to make predictions about future infectious disease risks. Proc Biol Sci, 366, 2045-2054.

XJ Technologies, 2007: AnyLogic 6 user's guide. XJ Technologies Company Ltd, St. Petersburg, Russian Federation

Table 6.1: Parameters used for system dynamic (SDM) and agent-based network (ABNM) modeling of influenza spread among swine farms.

Parameter	Value	Reference
1. Natural history of influenza infection of a farm (day)		
(a) Exposed- all farm types	3 days - SDM	Assumption
	Pert(1, 3, 5) - ABNMs	(Lange et al., 2009, Brookes et al., 2010, Vincent et al., 2010)
(b) Infectious period	25 days for all farm types in SDM	Assumption
(i) Sow	Pert (22, 25,30) in ABNMs	Generated from the individual-level parameters using WH 0.9.7 software†
(ii) Nursery	31 - exposed period in ABNMs	Assumption
(iii) Finisher	120 - exposed period in ABNMs	Assumption
(c) Recovered	Permanent for all farm types in SDM	
	Permanent for sow farms in ABNMs	
	14 days for nursery and finisher in ABNMs	
2. Contact frequency		
(a) SDM	0.143/day (once a week)	(Dorjee et al., 2013b)
(b) ABNMs		
(i) Sow to sow	0.143/day (once a week)	Assumption
(ii) Sow to nursery	0.286/day (twice a week)	(Dorjee et al., 2013b)
(iii) Sow to finisher	0.143/day (once a week)	Assumption
(iv) Nursery to finisher	0.143/day (once a week)	(Dorjee et al., 2013b)
(v) Finisher to sow	0.033/day (once a month)	(Torremorell et al., 2009)
3. Infectivity per contact (both SDM/ABNMs)		
(a) Infectivity by exposed- all farm types	0.1	Assumption
(b) Infectivity by infectious- all farms types	0.9	Derived as explained in the text
4. Number of links/farm	4	(Dorjee et al., 2013b)
5. Small-world network- probability of random re-wiring of long-range links	0.05; 0.1; 0.3	(Rahmandad and Sterman, 2008)
6. M parameter of the scale-free network	4	(Dorjee et al., 2013b)

†WH 0.9.7 is the software that simulate within-herd disease transmission stochastically and generates herd-level durations of disease states (Reeves et al., 2013).

Table 6.2: Summary results from the 22 simulated scenarios evaluating the effects of network structure on the spread and control of influenza among swine farms. The results of each scenario are summarized as median values (5^{th}–95^{th} percentiles) based on 500 iterations.

Models	Peak day	Peak day prevalence*	Epidemic size¥
A. Spread - without quarantine			
1. Infection seeded in a single randomly selected sow farm			
SDM	100	149	477
Random network	107 (6–359)[a]	18 (2–78)[a]	36 (2–196)[a]
Scale-free network	98 (7–357)[a,c]	22 (2–89)[a]	46 (2–203)[a]
Small-world network (0.05)	78 (8–213)[b]	43 (2–106)[b]	84 (3–228)[b]
Small-world network (0.1)	79 (9–245)[b]	40 (2–112)[b]	81 (3–244)[b]
Small-world network (0.3)	103 (10–322)[c]	49 (3–116)[b]	114 (3–257)[b]
2. Infection seeded in a maximally connected sow farm			
Random network	136 (8–353)[a]	29.5 (2–81)[a]	83 (3–209)[a]
Scale-free network	113 (8–361)[a,c]	34 (3–91)[a]	83 (4–224)[a, b]
Small-world network (0.05)	75 (10–222)[b]	49 (3–106)[b]	94 (4–237)[a, b]
Small-world network (0.1)	77 (11–257)[b]	45 (3–114)[b]	97 (3–245)[b]
Small-world network (0.3)	102 (8–302)[c]	59 (2–120)[b]	142 (2–259)[c]
B. Spread – assuming general quarantine			
1. Infection seeded in a single randomly selected sow farm			
SDM	61	20	49
Random network	89 (6–337)[a, b]	17 (2–56)[a]	36 (2–138)[a]
Scale-free network	85 (8–345)[b]	20 (2–58)[a]	42 (3–130)[a]
Small-world network (0.05)	70 (10–198)[c]	40 (3–66)[b]	79 (3–165)[b]
Small-world network (0.1)	72 (11–192)[a, c]	41 (2–67)[b]	82 (3–168)[b]
Small-world network (0.3)	80 (9–246)[a, b, c]	43 (2–74)[b]	96 (3–174)[b]
2. Infection seeded in a maximally connected sow farm			
Random network	102 (8–345)[a]	29 (2–60)[a]	73 (2–147)[a]
Scale-free network	82 (13–325)[a, d]	29 (3–61)[a]	66 (4–142)[b]
Small-world network (0.05)	68 (8–185)[b]	41 (3–68)[b]	80 (3–164)[a, c]
Small-world network (0.1)	66 (8–213)[b, c]	45 (2–71)[b ,c]	98 (2–172)[d]
Small-world network (0.3)	76 (10–268)[c, d]	48 (2–76)[c]	108 (2–179)[c]

*Peak day prevalence is the number of infectious farms on the peak day.
¥ Epidemic size is the total number of farms infected during the outbreak.
All model results summarized in the table excluded stochastic 'die-out' iterations (zero farm infected) of 500 runs.
Metrics with the same superscript letters amongst different ABNM within two settings of infection seeding are statistically not significant from one another.
SDM model could not be compared because it was of its deterministic nature with only one iteration.

Table 6.3: Summary results evaluating the effectiveness of targeted quarantine measures on the spread of the influenza among swine farms in a scale-free network. The results of each model are summarized as median values (5^{th}–95^{th} percentiles) values based on 500 iterations.

Models	Peak day	Peak day prevalence*	Epidemic size¥	Duration of outbreak (days)	No. of farms quarantined
1. Infection seeded in a single randomly selected sow farm					
Random quarantined	41 (7–145)[a]	12 (2–25)[a]	21 (2–43)[a]	260 (32–352)[a]	157 (0–290)[a]
Target farm ≥75^{th} percentile of links	22 (3–115)[b]	8 (2–13)[b]	12 (2–25)[b]	231 (39–353)[a]	109 (0–123)[b]
Target farm ≥95^{th} percentile of links	67 (6–323)[c]	14 (2–53)[c]	28 (3–135)[c]	228 (13–356)[a]	21 (0–24)[c]
2. Infection seeded in a maximally connected sow farm					
Random quarantined	38 (9-111)[a]	15 (3–31)[a]	26 (3–54)[a]	275 (29–356)[a]	191 (0–308)[a]
Target farm ≥75^{th} percentile of links	18 (5-102)[b]	8 (3–14)[b]	13 (3–27)[b]	234 (40–344)[b]	110 (0–123)[b]
Target farm ≥95^{th} percentile of links	55 (5-340)[c]	14 (2–58)[c]	27 (2–145)[b]	236 (17–355)[b]	21 (0–24)[c]

*Peak day prevalence is the number of infectious farms on the peak day.
¥ Epidemic size is the total number of farms infected during the outbreak
All model results summarized in the table excluded stochastic 'die-out' iterations (zero farm infected) of 500 runs;
Metrics with the different superscript letters amongst different ABNM within two settings of infection seeding are statistically significant from one another.

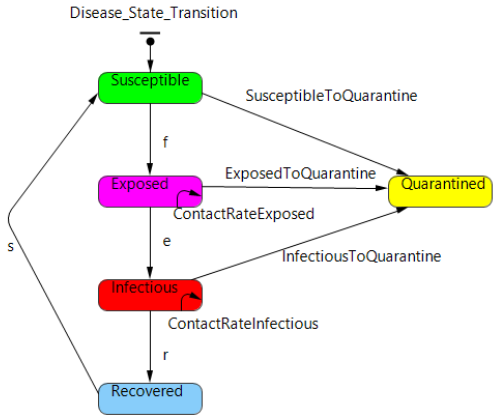

Figure 6.1: Influenza infection transition chart for all farms present in the agent-based network models. Key: f, e, r and s represent instances of exposure, or of transitions from exposed to infectious, from infectious to recovered, and from recovered to susceptible states.

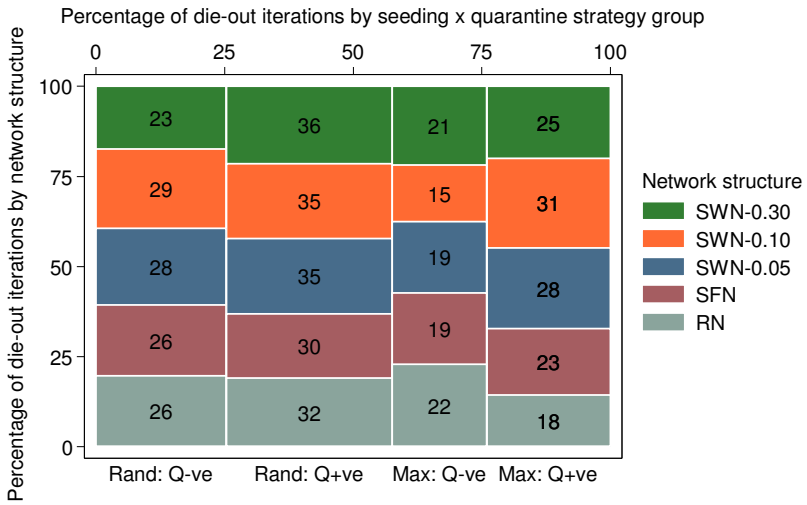

Figure 6.2: Percentage of iterations with stochastic 'die-outs' (zero units infected) in each of the five agent-based network models of influenza spread and general quarantine measures (quarantine implemented as reduction in contact rate between farms) under two settings of infection seeding into a sow farm. For each iteration of the simulation an infection was seeded into either a single randomly selected sow farm or into the sow farm with the maximum number of links. Each model was simulated for 500 iterations. Key: RN = random network model; SFN = scale-free network model; SWN-0.05 to SWN-0.30 = small-world network models with the probabilities of long-range links equal to 5%, 10% and 30%, respectively; Rand = seeding the infection in a randomly selected sow farms; Max = seeding in a sow farm with the maximum number of links; Q-ve = spread scenario (without quarantine measure); Q+ve = with quarantine measure.

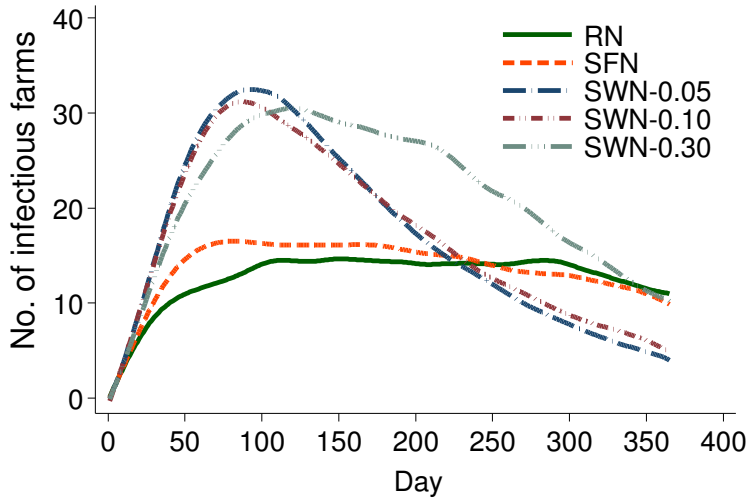

Figure 6.3: Epidemic curves of influenza spread in different network models when the infection seeded in a maximally connected sow farm. Key: RN = random network model; SFN = scale-free network model; SWN-0.05 to SWN-0.30 = small-world network models with the probabilities of long-range links equal to 5%, 10% and 30%, respectively.

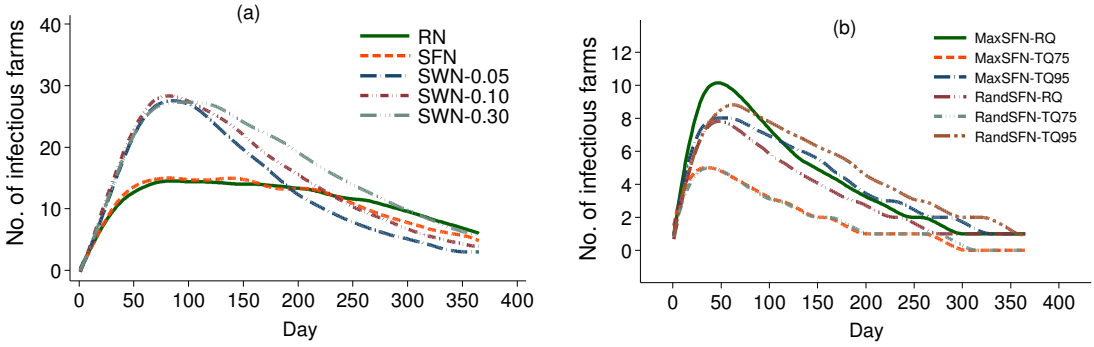

Figure 6.4: Epidemic curves of influenza spread: (a) in different network models under a general quarantine strategy when infection was seeded in a maximally connected sow farm, and (b) SFN network models under a targeted quarantine strategy under both types of infection seeding. Note difference in y-axis scales between (a) and (b). Key: RN = random network model; SFN = scale-free network model; SWN-0.05 to SWN-0.30 = small-world network models with the probabilities of long-range links equal to 5%, 10% and 30%, respectively; MaxSFN and RandSFN = infection seeded in a maximally connected and randomly selected sow farm respectively; RQ= farms quarantined randomly; TQ75 and TQ95 = targeted quarantine of all farms with number of links ≥75th and 95th percentiles distribution respectively.

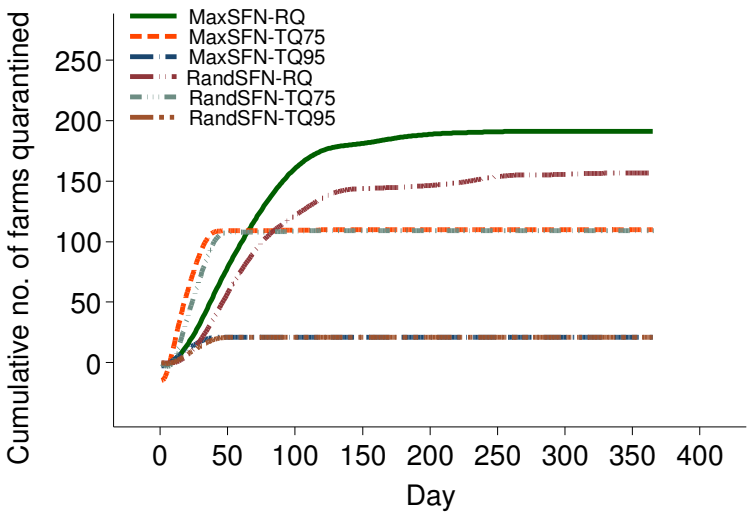

Figure 6.5: Cumulative number of farms quarantined under different quarantined strategies. Key: Max and Rand = infection seeded in a maximally connected and randomly selected sow farm respectively; SFN = scale-free network model; RQ= farms quarantined randomly; TQ75 and TQ95 = targeted quarantine of all farms with number of links ≥75th and 95th percentiles distribution respectively.

Chapter 7
Conclusions and Future Directions

In this thesis a systematic review of modeling methods and approaches including existing gaps in the knowledge of transmission dynamics of zoonotic influenza in animals and humans, particularly at the animal-to-human interface, was conducted. Building on this review, the effect of the transmissibility of the pH1N1 virus at the swine-human interface and the effectiveness of control strategies against its spread in swine and human populations, were evaluated as a case study of zoonotic disease modeling. Unlike many other zoonotic modeling studies, in which the study of transmission dynamics and control measures are restricted to either reservoir animal or human hosts, this study adopted a one-health approach by simultaneously modeling the spread of pH1N1 among and between swine and human populations using NAADSM software. Furthermore, network analyses of swine shipments among farms, and between farms and processing units, and an assessment of the effects of network structures on the spread and control of the pH1N1 virus in swine populations were carried out to inform some of the knowledge gaps identified by the systematic review. The main findings of these studies, their relevance to supporting policy decisions, the associated limitations, and future directions in research that is required to address some of the critical issues identified are presented in the following sections.

7.1 Chapter 2

A synopsis of modeling methods and approaches, together with software used for modeling the spread of zoonotic influenza viruses in animals and humans, particularly those related to the animal-human interface, was presented in this chapter. A significant

increase in the application of modeling research to assess patterns of influenza spread and the effectiveness of a single or a combination of intervention strategies in human populations was observed. The modeling approaches and methods have also advanced significantly in terms of complexity, from simple deterministic to more stochastic and individual-based models, in an attempt to improve the validity of the models' predictions. In contrast, the application of modeling research to influenza in animals (including birds) and particularly at the animal-human interface was limited. These findings appear to be consistent across all zoonotic diseases, where most studies being restricted to exploring the dynamics of zoonoses in a single host species, either in the reservoir animal species or human populations (Lloyd-Smith et al., 2009). Significant gaps in knowledge around the frequency at which novel strains of virus evolve in pigs, the farm-level natural history of influenza infection, incidences of influenza transmission between farms and between swine and humans were clearly evident. This is disconcerting given the fact that swine have been recognized as a potential host for the generation of novel influenza viruses, and because influenza viruses, such as the pH1N1 virus, are easily transmissible between swine and humans. This review contributed to the existing literature by providing both a source of references for a wide-range of modeling approaches and a summary of important disease spread and intervention parameters extracted from primary research.

7.2 Chapter 3

The research in this chapter evaluated the effects of the transmissibility of the pH1N1 virus at the swine-human interface on its spread in the swine and human populations in general, while accounting for the different percentages of SWH units initially immune through vaccination. This study undertook a unique approach by simulating the spread of pH1N1 at the swine herd and household levels, instead of at the individual pig or person level. In addition, the SWH units served as a bridging population for the spread of the virus between swine herd and human household populations.

Given the assumptions specified in the models, the results showed that minimizing the influenza transmissibility at the swine-human interface and targeted vaccination of swine workers had significant beneficial effects for all the outcome measures. However, to achieve these beneficial effects the transmissibility of the virus from humans to animals or both humans to animals and animals to humans had to be reduced to the low level for SH (that is at the LL, ML and HL level) and household units (at the LL), respectively. As it was expected, reducing the transmissibility of the virus significantly prolonged the time to peak epidemic day, decreased peak prevalence and increased the likelihood of stochastic 'die-outs'. Furthermore, the size of the epidemics decreased in SH and SWH populations. Another notable result was that decreasing the transmissibility of the virus at the swine–human interface to LL had little or negligible impact on the size of the epidemic in the RH and UH populations. This is because the disease once introduced would spread in these household populations independent of its

transmission dynamics in SH and SWH units given the relatively larger numbers of RH and UH units, and the higher contact rates among those units. Although the results observed in this study may vary by the population structure, we would expect a similar trend as the household sizes and contact rates between RH, UH, and RH and UH would be relatively higher than SH or SWH in general. Therefore, other appropriate control strategies to prevent or minimize the spread from SWH to RH and UH needs to be implemented in combination with the lowering of the transmissibility of the virus at the interface.

The epidemiological implication of delaying the time to peak epidemic day is that this provides more time for the concerned authorities to mobilize resources and implement appropriate response measures, such as the delivery of antivirals, vaccination, or other social distancing measures. Furthermore, reducing the peak prevalence should reduce the extent of disease control activities (such as movement control and vaccination in animals) required, including the burden on health care facilities.

This study emphasised the importance of lowering the transmissibility of the virus at the swine-human interface to a low level. This can be achieved through several mechanisms, including: following good personal hygiene, avoiding direct contacts with sick pigs, using gloves and not smoking while working with pigs (Ramirez et al., 2006), abstaining from work or avoiding contact with pigs when suffering from influenza like illnesses, and implementing strict farm biosecurity practices. As significant differences

in the outcome measures were observed between low (0.024) and medium (0.3) to high (1.0) levels of the transmissibility of the virus at the interface, further sensitivity analysis needs to be carried out between the low and medium range of values to determine the threshold level below which significant beneficial impacts can be expected to occur.

The targeted vaccination of SWH had a significant beneficial effect on all the outcome metrics. However, significant positive effects were only consistently observed once 60% coverage had been reached. The effects of vaccination were largest in SWH followed by SH and to a lesser extent in the RH populations. However, the effect was negligible for UH population, likely for similar reasons to those mentioned for the transmissibility of the virus above. We assumed that vaccine that would confer 100% protection was available prior to the influenza outbreak. Questions remain as to whether such a vaccine would be readily available during the emergent phase of a novel virus. If a limited amount of such vaccine were to be available early on in an outbreak, targeting swine workers in cases where the virus was of swine origin would prove beneficial. However, once the virus had been introduced into RH and UH populations, the results suggested that targeting SWH alone would not be effective in containing the spread of the disease.

7.3 Chapter 4

This chapter of the thesis evaluated the effectiveness of various combinations of speed of detection of an outbreak, quarantine, movement control and ring vaccination strategies. Three levels of the speed of detection of an outbreak (slow, moderate or fast;

meaning that 98% of infected units were detected within 5, 10 or 20 days, respectively), two types of quarantine strategies (no-zone strategy where only the detected units were quarantined, or with-zone strategy where all units around 3 km radius of a detected unit were quarantined), two levels of effectiveness of movement control (less effective or effective where both movement restriction strategies achieved reduction of 95% of direct and 80% of indirect contact rates in less than 10 or 5 days, respectively), and three vaccination strategies (no-ring vaccination, ring vaccination with slow or fast triggers, where the vaccination of all susceptible units within a radius of 5 km was triggered upon detecting ≥25 or ≥5 infected units, respectively). In all cases the effectiveness of combinations of these strategies against the simultaneous spread of pH1N1 virus within and between swine and human populations was evaluated.

Results indicated that a combination of moderate to fast speed of the detection, combined with the effective quarantine of detected units alone, would contain the outbreak within the swine population in most of the simulated outbreaks. However, zone-based quarantine was a better strategy when the speed of detection was delayed by approximately 2–3 weeks (slow detection). These findings were consistent with other studies that evaluated similar control strategies (Ferguson et al., 2005, Longini et al., 2005, Shaban et al., 2009). The use of ring vaccination had no added beneficial impact. Therefore, these findings underscore the necessity of having effective surveillance in place to detect the disease as early as possible. Having effective surveillance and quarantine strategies in place will avoid the necessity of resorting to more expensive

ring vaccination measures. It could be argued that even the slow detection level defined in this study was relatively effective because in reality it may take from several weeks to months before a novel influenza virus is recognized as a potential pandemic threat. Its effective transmission from person to person would have to be known before serious public health intervention measures are initiated.

7.4 Modeling assumptions, limitations and the feasibility of NAADSM

Several simplifying assumptions were made as in other modeling studies of this domain. The detailed discussions on the assumptions and limitations including those attributed to using NAADSM were discussed in Chapters 3 and 4, and only the important ones are highlighted in this section.

One of the main limitations, rather a debatable one is using farms and households as the unit of simulation based on the design of NAADSM. While it is the most common approach to model livestock diseases at a farm level, most modeling studies in human populations are simulated at the individual level. However, some studies have suggested modeling a disease spread at the household level as a better alternative for diseases like pandemic influenza (Ferguson et al., 2005, Longini et al., 2005, Wu et al., 2006, Fraser, 2007). This approach has been justified on the basis that most influenza transmission occurs within a household and cases tend to cluster locally. In addition, it is more practical and effective to target implementation of both public health and pharmaceutical intervention measures at the household level or all households within a zone of a certain radius than at the individual level. Therefore, a choice as to the

granularity of simulation unit and evaluation of spread and control strategies adopted in our studies are consistent with the approaches highlighted by these studies. This approach is one of the fundamental assumptions required for NAADSM to be used for modeling directly transmitted zoonotic diseases.

The studies of Chapters 3 and 4 also made an assumption that a farm or household was infectious from the time a single pig or individual on a farm or household became infectious, an inherent assumption inbuilt into the NAADSM version 3.1.24. In reality all animals on a farm or individuals in a household may not become infected, though some studies have shown that the large majority of animals do become infected during pH1N1 outbreaks on farms (Howden et al., 2009, OIE, 2009-2010, Pasma and Joseph, 2010). The household secondary attack rates for pH1N1 estimated ranged from 4–50 % (Cauchemez et al., 2009, Ghani et al., 2009, Yang et al., 2009, van Gemert et al., 2011). Accordingly, this assumption might have led to an overestimation of the spread of the disease in the SH and household populations. Given a contact, the probability of transmission will likely be influenced by the within-farm or within-household prevalence including size of animal shipments for direct contacts between SH units, which were not considered because of limitation of the NAADSM version used in these studies. In addition, a 100% probability of transmission per contact was assumed among SH. Therefore the transmission rate may have been overestimated.

Contrary to the previous situation, the contact rates among households were assumed equal to the average daily contact rate of an individual person for UH units, or half this

rate for SWH and RH units. This might have underestimated the spread of the disease because each household has, on average three members, and therefore the actual contact rate between households would have been higher. However, the references (Mossong et al., 2008, Lee et al., 2010) from which these contact rates were extracted did not specify what proportion of a daily average contact rate is between the members of the same household, or among and between different occupational groups (e.g. swine workers, rural non-swine workers or urban households). Therefore, the magnitude and direction of bias in the estimates of the spread of the disease in these populations could not be predicted.

For simplicity all swine farms were treated as a homogeneous population with random mixing, but in reality the susceptibility and contacts will likely vary by farm types (sow, nursery or finishing types), as observed for classical swine fever (Dürr et al., 2013) and in Chapter 5 of this thesis. Similarly, the individual's susceptibility to influenza may vary by age and family size (Cauchemez et al., 2009, Yang et al., 2009, van Gemert et al., 2011), and the contact structure which were not considered. The assumptions of homogeneous population of swine herds or households and a random mixing might have overestimated the size of outbreaks in general. While different swine production types could be explicitly modeled in NAADSM, it does not have the flexibility to incorporate individual level heterogeneity within a household for parameters such as the contact rates, risk or susceptibility to a zoonotic agent, which

may vary significantly according to social demographics such as age, gender, race and occupation.

In addition, NAADSM lacks the feature to explicitly represent different contact network structures such as scale-free or small-world topologies observed in real-world which influences the speed and control of a disease spread in a population. It is also not possible to assign more than a single location to each unit in NAADSM, in contrast to many human disease spread models where individuals are assigned to two or more locations, such as at home, school/workplace, other places of social gathering. Furthermore, in NAADSM a disease transmission is simulated not only based on the contact rate and transmission probabilities, but also as a function of spatial distance between source and recipient units. However, households or people even in close geographic proximity may not have any contact between one another to facilitate the influenza spread. Spatial location becomes largely irrelevant unless a disease spreads locally through aerosol transmission. The NAADSM version used in these studies also lacks the capability to seed the infection randomly in a population for each iteration of the scenario. This feature is important as the speed and extent of spread of a disease including stochastic 'die-out' fraction will be affected to a certain degree by the density of population around the index unit. It is possible to select a unit randomly for seeding the infection for each iteration but was not done due to practical difficulties when running thousands of iterations. In addition, we cannot seed the infection repeatedly from the external source into the study population which is important for diseases like

influenza particularly in household populations. Future version of NAADSM may explore incorporating these features. Another major limitation of the personal computer version of NAADSM observed in this study is the time taken to simulate populations of a significant size. Despite being run on a powerful Windows-based personal computer machine the simulation of this study population with 30,195 units took 4 days to complete around 100 iterations and did not progress further and crashed. Therefore, we resorted to the super-computer version for running our simulations.

The role of other occupational groups such as veterinarians, abattoir workers, and swine transporters who come into contact with swine, and who may play an important role in influenza spread were not considered. Similarly the role of live swine markets was not considered. Therefore, these assumptions might have underestimated the spread of the influenza in the study populations to a certain extent.

Regardless of these limitations, we found that NAADSM can be used to model the spread and control of contagious zoonotic diseases like influenza under similar simplifying assumptions to those adopted in this study. This is not surprising given that NAADSM was originally built to model spread of FMD between groups of different susceptible mammalian species (e.g. bovine, porcine, ovine) and production types (e.g. beef, cow calf versus dairy cattle, etc.). Therefore, if one considers UH and RH as just other types of groups of mammals, then NAADSM is as well of better suited to model the human-animal interface of zoonotic disease spread. However, its feasibility needs to be further validated using models calibrated with more accurate farm and household

level parameters and influenza outbreak data. For this a good quality information on the natural history of influenza infection at the farm and household levels, its spread or reproductive numbers of both within and between farms and households, and contact rates between household types are required, which are lacking currently. The NAADSM is a sophisticated, flexible and user-friendly framework for modeling. It is particularly user friendly to people with a biology background who do not possess strong mathematical or computer programming skills (as are typically required to make appropriate use of other modeling software).

In our studies, the feasibility of using NAADSM for modeling zoonotic diseases was investigated in the context of directly transmitted pathogens where a pathogen spreads easily both within and between species simultaneously, and in cases where simulating the disease spread at aggregate level such as farm or a household level is reasonable. It is not suitable for modeling vector-born, foodborne and other zoonotic diseases where the unit of simulation had to be at the individual animal or person level. For this major structural changes in NAADSM would be required. Other more flexible and powerful modeling software like AnyLogic® used for the study described in Chapter 6 provide a better alternative for modeling all types of zoonoses and for all purposes. AnyLogic® is powerful multi-methods modeling software that can be used to build discrete event, system dynamic, agent-based/individual-based, or hybrid of any of these models including spatially explicit and network-based models. However, AnyLogic® is not easily accessible and user friendly to field epidemiologists as it requires a high-level of

training and support of information technology professionals besides being relatively expensive software. Therefore, it seems imperative to invest in upgrading software like NAADSM to incorporate flexibility to overcome the deficiencies highlighted above to develop it into generic zoonotic diseases modeling framework.

7.5 Chapter 5

This chapter of this thesis, a network analysis of the swine shipments among farms was conducted. The result showed the heterogeneity in the contact frequency among and between swine farm types. The network also demonstrated scale-free and small-world topologies. Furthermore, this study also included network analysis of swine shipments from farms to processing units using the directed two-mode network approach. The epidemiological implications of the network metrics were presented in detail in the Chapter 5, including potential use of two-mode network analysis between farms and slaughterhouses. Although not a comprehensive study in terms of province or country wide coverage, the estimates of the network and farm level metrics were found similar to other studies. This study provides a number of useful epidemiological information for understanding the patterns of disease spread, parameters required for modeling and supporting risk-based disease management in swine first time in Ontario, Canada.

7.6 Chapter 6

In this chapter, the effects of network structures (RN, SFN and SWN) on the spread and control of pH1N1 virus in a specialized multi-site AIAO swine production system using the agent-based network modeling approach was evaluated. The results showed the

speed and the size of the influenza outbreaks in the RN and SFN models were similar. In addition, long-range links present in SWN models allowed the disease to spread faster and with greater outbreak size than in either SFN or RN models. This is contrary to the previous findings in both animal and human populations (Keeling and Eames, 2005, Shirley and Rushton, 2005, Rahmandad and Sterman, 2008), where diseases spread faster in SFN followed by RN and SWN models. This difference might be due to the combination of small network size and relatively lower value of the average number of links per farm used in our study, resulting in a relatively smaller magnitude of the SFN effect than a SWN effect on the spread of influenza in this study population. Therefore, future models should incorporate an appropriate network structure to improve the validity of the disease spread models. The quarantine strategy that quarantined all farms with the number of links ≥75th percentile distribution had the maximum benefit followed by randomly targeted quarantine strategy and the quarantine strategy targeting only farms with the number of links ≥95th percentile distribution. However, the cost benefit of quarantining more number of farms vis-à-vis cost saved through minimizing losses from a disease outbreak should be assessed to decide on appropriate control strategies. To our best knowledge this is the first study conducted for assessing the effect of network structure on influenza spread in a swine population.

7.7 Future directions

The future directions proposed in this section are based on gaps in knowledge and information identified through the systematic review as well as from results in the modeling studies outlined above.

- It is apparent that modeling research on influenza transmission dynamics in animals (including birds) and at the animal-human interface has been grossly neglected. As such, more modeling research needs to be conducted. This is imperative given the continued threat posed by the repeated emergence of pandemic influenza viruses and the potential role animals (particularly swine) can play in generating novel influenza viruses.
- One of the main limitations of zoonotic modeling studies described in Chapters 3, 4, and 6 has been the lack of information on the farm-level natural history of influenza infection and farm-to-farm spread parameters through direct contact (shipment of animals between farms) and indirect contact (through movement of swine workers, veterinarians, and other fomites) to calibrate the models. Therefore some studies need to be conducted to estimate these parameters. It is possible that some of the information are available but have not been reported in a form usable for modeling work. More representative studies to estimate different stages of pH1N1 or infection with other influenza viruses at the farm level may provide useful information to parameterize of models in the future.

- Some prospective studies also need to be conducted to quantify the transmissions of pH1N1 from swine to human and human to swine as it is one of the main transmission parameters required for modeling.
- Some surveys may also be conducted to estimate the contact frequency among different occupations of people similar to those reported by Mossong et al. (2008)
- Future studies need to investigate whether the findings of Chapters 3 and 4 are consistent across all plausible ranges of the infectious duration of the virus, transmission probabilities of the diseases in swine and humans, the effect of further delaying the speed the detection, and reducing the effectiveness of movement restrictions through adequate sensitivity analyses.
- Future modeling research could also investigate the effect of vaccinating similar proportions of the rural and/or urban populations in addition to swine workers for controlling influenza pandemic.
- It is recommended that a more extensive and representative swine shipments network analysis study covering a larger area and incorporating both direct and indirect contacts related to swine industry be initiated to validate the estimates presented in this thesis.
- In the agent-based network models study in Chapter 6, all the links were treated as binary and static, and the transmission through indirect contacts such as movement of people and other fomites including their effect in other settings of

swine production systems were not considered. Therefore, future studies may investigate these findings further using weighted and dynamic network similar to study conducted by Vernon and Keeling (2009), and in other swine management systems. This is also one of the limitations of the NAADSM models explained earlier.

- It is worthwhile to invest in upgrading the user friendly software like NAADSM to incorporate more flexibility and features to overcome the deficiencies highlighted above to develop it into a generic zoonotic diseases modeling framework.

7.8 Concluding remarks

The work presented in this thesis contributes to the literature by providing an overview of modeling approaches, methods and software used for influenza modeling in animal and human populations. In addition, key disease spread and intervention parameters used for modeling influenza viruses are consolidated for ready reference in future works. It also highlighted the huge lacunae existing in the modeling research in animals and animal-human interface. Priority needs to be accorded to address some of these deficiencies given the rising incidence of zoonotic diseases throughout the world. The importance of reducing the transmissibility of the influenza at the animal-human interface, early detection through effective surveillance mechanisms, and effective quarantine measures for controlling the outbreaks were highlighted. Furthermore, the feasibility of using a user friendly modeling framework designed for field

epidemiologists (NAADSM) was investigated, and suggestions to further upgrade it into a generic zoonotic modeling framework were provided. Other contributions of this thesis include estimation of useful network metrics and parameters required for understanding the patterns of disease spread, and for supporting modeling research and risk-based disease management decisions in swine populations. We have also developed different network structures based on multiple production types for the first time in AnyLogic (the default network feature is limited to single agent type). This study demonstrated the importance of incorporating appropriate network structure explicitly to improve the validity of a model's predictions, and the benefits of the targeted control strategies.

Lastly, although, simulation models are useful tools and are increasingly being used to support policy decisions in the disease prevention and management, a cautionary reminder by Kao (2002) that, 'all theoretical models are only one aspect to providing good scientific advice, augmenting experimental investigation and the good collection and analysis of epidemiological data' must be noted. Thus, research priority needs to be given to the collection, analysis and reporting of epidemiological data in formats that can be used within modeling research, particularly for important zoonotic diseases at the animal-human interface.

7.9 References

Cauchemez, S., C. A. Donnelly, C. Reed, A. C. Ghani, C. Fraser, C. K. Kent, L. Finelli and N. M. Ferguson, 2009: Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. N. Engl. J. Med., 361, 2619-2627.

Dürr, S., H. zu Dohna, E. Di Labio, T. E. Carpenter and M. G. Doherr, 2013: Evaluation of control and surveillance strategies for classical swine fever using a simulation model. Prev. Vet. Med., 108, 73-84.

Ferguson, N. M., D. A. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn and D. S. Burke, 2005: Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature, 437, 209-214.

Fraser, C., 2007: Estimating individual and household reproduction numbers in an emerging epidemic. PLoS One, 2, e758.

Ghani, A., M. Baguelin, J. Griffin, S. Flasche, A. J. van Hoek, S. Cauchemez, C. Donnelly, C. Robertson, M. White, J. Truscott, C. Fraser, T. Garske, P. White, S. Leach, I. Hall, H. Jenkins, N. Ferguson and B. Cooper, 2009: The early transmission dynamics of H1N1pdm influenza in the United Kingdom. PLoS Curr., 1, RRN1130.

Howden, K. J., E. J. Brockhoff, F. D. Caya, L. J. McLeod, M. Lavoie, J. D. Ing, J. M. Bystrom, S. Alexandersen, J. M. Pasick, Y. Berhane, M. E. Morrison, J. M. Keenliside, S. Laurendeau and E. B. Rohonczy, 2009: An investigation into human pandemic influenza virus (H1N1) 2009 on an Alberta swine farm. Can. Vet. J., 50, 1153-1161.

Kao, R. R., 2002: The role of mathematical modelling in the control of the 2001 FMD epidemic in the UK. Trends Microbiol., 10, 279-286.

Keeling, M. and K. Eames, 2005: Networks and epidemic models. J. R. Soc. Interface, 2, 295 - 307.

Lee, B. Y., S. T. Brown, P. Cooley, M. A. Potter, W. D. Wheaton, R. E. Voorhees, S. Stebbins, J. J. Grefenstette, S. M. Zimmer, R. K. Zimmerman, T. M. Assi, R. R. Bailey, D. K. Wagener and D. S. Burke, 2010: Simulating school closure strategies to mitigate an influenza epidemic. J. Public Health Manag. Pract., 16, 252-261.

Lloyd-Smith, J. O., D. George, K. M. Pepin, V. E. Pitzer, J. R. Pulliam, A. P. Dobson, P. J. Hudson and B. T. Grenfell, 2009: Epidemic dynamics at the human-animal interface. Science, 326, 1362-1367.

Longini, I. M., Jr., A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D. A. Cummings and M. E. Halloran, 2005: Containing pandemic influenza at the source. Science, 309, 1083-1087.

Mossong, J., N. Hens, M. Jit, P. Beutels, K. Auranen, R. Mikolajczyk, M. Massari, S. Salmaso, G. S. Tomba, J. Wallinga, J. Heijne, M. Sadkowska-Todys, M. Rosinska and W. J. Edmunds, 2008: Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med., 5, e74-e74.

OIE, 2009-2010: World Animal Health Information Database: Weekly disease information. Available at http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/reportarchive (accessed on 22 April 2010). Paris.

Pasma, T. and T. Joseph, 2010: Pandemic (H1N1) 2009 infection in swine herds, Manitoba, Canada. Emerg. Infect. Dis., 16, 706-708.

Rahmandad, H. and J. Sterman, 2008: Heterogeneity and network structure in the dynamics of diffusion: Comparing agent-based and differential equation models. Manage Sci, 54, 998–1014.

Ramirez, A., A. W. Capuano, D. A. Wellman, K. A. Lesher, S. F. Setterquist and G. C. Gray, 2006: Preventing zoonotic influenza virus infection. Emerg. Infect. Dis., 12, 997.

Shaban, N., M. Andersson, A. Svensson and T. Britton, 2009: Household epidemics: modelling effects of early stage vaccination. Biom J, 51, 408-419.

Shirley, M. D. F. and S. P. Rushton, 2005: The impacts of network topology on disease spread. Ecol. Complexity, 2, 287-299.

van Gemert, C., M. Hellard, E. S. McBryde, J. Fielding, T. Spelman, N. Higgins, R. Lester, H. Vally and I. Bergeri, 2011: Intrahousehold transmission of pandemic (H1N1) 2009 virus, Victoria, Australia. Emerg. Infect. Dis., 17, 1599-1607.

Vernon, M. C. and M. J. Keeling, 2009: Representing the UK's cattle herd as static and dynamic networks. Proc. R. Soc. Lond. B. Biol. Sci., 276, 469-476.

Wu, J. T., S. Riley, C. Fraser and G. M. Leung, 2006: Reducing the impact of the next influenza pandemic using household-based public health interventions. PLoS Med., 3, e361-e361.

Yang, Y., J. D. Sugimoto, M. E. Halloran, N. E. Basta, D. L. Chao, L. Matrajt, G. Potter, E. Kenah and I. M. Longini, Jr., 2009: The transmissibility and control of Pandemic Influenza A (H1N1) virus. Science, 326, 729-733.

Appendix A

Supplementary tables

Table S1: List of articles that used different methods for modeling the spread of zoonotic influenza viruses in human and animal populations to address various research questions.

Species and spread type	Model type	Questions of interests	Article
A. Human-human	1. Deterministic agent-based/ individual-based model	I[1]; IS[2]	(Kitching et al., 2006)[1]; (Hartvigsen et al., 2007)[2]
	2. Deterministic heterogeneous mixing compartmental model	I[1]; IM[2]; IS[3]; P[4]	(Gani et al., 2005, Duerr et al., 2007b, Tennenbaum, 2008, An der Heiden et al., 2009, Medlock and Meyers, 2009, Tuite et al., 2009, Tsai et al., 2010, Tuite et al., 2010a)[1]; (Larson, 2007, Nigmatulina and Larson, 2009)[2]; (Roberts et al., 2007, Wein and Atkinson, 2009)[3]; (Fraser et al., 2009, Tuite et al., 2010b)[4]
	3. Deterministic heterogeneous mixing & spatially explicit compartmental model	IMS	(Lunelli et al., 2009)
	4. Deterministic homogeneous mixing compartmental model	I[1]; IM[2]; IS[3]; MS[4]; P[5]; PS[6]; S[7]; T[8]	(Sattenspiel and Herring, 2003, Hollingsworth et al., 2006, Gardam et al., 2007, Nuño et al., 2007a, Nuño et al., 2007b, Arinaminpathy and McLean, 2008a, Arino et al., 2008, Gumel et al., 2008, Nuño et al., 2008)[1]; (Vardavas et al., 2007)[2]; (Chowell et al., 2006b, Flahault et al., 2006)[3]; (Brauer, 2008)[4]; (Mills et al., 2004, Chowell et al., 2006a, Sertsou et al., 2006, Chowell et al., 2007a, Chowell et al., 2007b, Chowell et al., 2008b)[5]; (Massad et al., 2007)[6]; (Flahault et al., 1994, Grais et al., 2003, Grais et al., 2004, Lavenu et al., 2004, Rios-Doria and Chowell, 2009)[7]; (Eichner et al., 2007)[8]
	5. Deterministic network model	M	(Aparicio and Pascual, 2007)
	6. Stochastic agent-based/ individual-based model	I[1]; IM[2]; IP[3]; IS[4]; M[5]; MS[6]; S[7]; T[8];	(Ferguson et al., 2006, Wu et al., 2006, van den Dool et al., 2008, Basta et al., 2009, Lee et al., 2009a, Sypsa et al., 2009, Milne et al., 2010)[1]; (Das et al., 2008)[2]; (Yang et al., 2009, Yasuda and Suzuki, 2009)[3]; (Germann et al., 2006, Ohkusa and Sugawara, 2007, Ciofi degli Atti et al., 2008, Sypsa and Hatzakis, 2009)[4]; (Fraser, 2007, Tsai et al., 2010)[5]; (Carpenter and Sattenspiel, 2009)[6]; (Ohkusa and Sugawara, 2009)[7]; (Hanley, 2006, Feighner et al., 2009)[8];
	7. Stochastic agent-based/individual network model	I[1]; IS[2]; MT[3]; PS[4]	(Davey and Glass, 2008, Perlroth et al., 2010)[1]; (Carrat et al., 2006b, Duerr et al., 2007c)[2]; (Chao et al., 2010)[3]; (Ajelli and Merler, 2008)[4]

Key: I = evaluate different types of intervention measures; M = describe new modeling methods, techniques and approaches; P = parameter estimation; S = evaluate spread of influenza; T = development of modeling platforms or tools (T). Combination of these letters indicates more than one research questions of interest. Where there are more than one set of combination of question of interests for application of a particular model, superscripts on question of interests correspond to superscripts of respective articles.

Table S1: (continued)

Species and spread type	Model type	Questions of interests	Article
	8. Stochastic agent-based/individual-based spatially explicit model	I[1];	(Ferguson et al., 2005, Halloran et al., 2008)[1];
	9. Stochastic heterogeneous mixing compartmental model	I[1]; IM[2]; IMS[3;] IS[4]; M[5];	(Halloran et al., 2002, Weycker et al., 2005, Glass and Barnes, 2007, Haber et al., 2007)[1]; (Shaban et al., 2009)[2]; (Gojovic et al., 2009)[3]; (Longini et al., 2004, Rizzo et al., 2008)[4]; (Addy et al., 1991)[5];
	10. Stochastic heterogeneous mixing gravity model	S	(Boni et al., 2009)
	11. Stochastic homogeneous mixing compartmental model	I[1]; P[2];	(Epstein et al., 2007, Wood et al., 2007, Xu et al., 2007)[1]; (Lessler et al., 2007)[2]
	12. Stochastic metapopulation model	I[1]; IS[2]; MS[3]	(Cooper et al., 2006)[1]; (Colizza et al., 2007, Flahault et al., 2009)[2]; (Balcan et al., 2009)[3]
	13. Stochastic network model	I[1]; IS[2]	(Glass et al., 2006)[1]; (Hsu and Shih, 2010)[2]
	14. Stochastic spatially explicit metapopulation model	PS	(Colizza et al., 2009b)
	15. Stochastic spatially explicit network model	I	(Longini et al., 2005)
B. Bird-bird	1. Deterministic homogeneous mixing compartmental model	IS[1]; IM[2]; P[3]; S[4]	(Elbakidze, 2008)[1]; (Iwami et al., 2009)[2]; (Ward et al., 2009)[3]; (Bos et al., 2007, Guberti et al., 2007)[4]
	2. Stochastic agent-based/individual-based model	IS	(Savill et al., 2006)
	3. Stochastic heterogeneous mixing compartmental model	S	(Bavinck et al., 2009)
	4. Stochastic homogeneous mixing compartmental model	P[1]; IP[2]	(van der Goot et al., 2003)[1]; (van der Goot et al., 2005)[2]
	5. Stochastic spatially explicit agent-based/individual-based model	I	(Le Menach et al., 2006)
	6. Stochastic spatially explicit network model	IS	(Sharkey et al., 2008)
C. Bird-bird and bird-human	1. Stochastic agent-based/individual-based spatially explicit model	MT	(Rao et al., 2009)
	2. Deterministic homogeneous mixing metapopulation model	IM	(Arino et al., 2007)
D. Bird-bird, bird-human and human-human	1. Deterministic homogeneous mixing compartmental model	M	(Iwami et al., 2007, Kim et al., 2010)
E. Animal-animal, animal-human, human-human and human-animal	1. Deterministic multi-host compartmental model	IMS	(Saenz et al., 2006)

Table S2: List of articles that used different modeling methods for assessing various intervention strategies against zoonotic influenza in human and animal populations

Species and spread type	Model type	Interventions	Articles
A. Human-human	1. Deterministic agent-based/individual-based model	V	(Kitching et al., 2006, Hartvigsen et al., 2007)
	2. Deterministic heterogeneous mixing compartmental model	A[1]; AD[2]; ADS[3]; D[4]; T[5]; V[6]	(Gani et al., 2005)[1]; (Duerr et al., 2007a, An der Heiden et al., 2009)[2]; (Roberts et al., 2007)[3]; (Larson, 2007, Wein and Atkinson, 2009)[4]; (Nigmatulina and Larson, 2009)[5]; (Medlock and Meyers, 2009, Tuite et al., 2009, Tuite et al., 2010a)[6]
	3. Deterministic heterogeneous mixing & spatially explicit compartmental model	ASV	(Lunelli et al., 2009)
	4. Deterministic homogeneous mixing compartmental model	A[1]; AD[2]; ADS[3]; ADSV[4]; ADTV[5]; AV[6]; D[7]; T[8]; V[9]	(Gardam et al., 2007, Brauer, 2008, Arinaminpathy and McLean, 2009)[1]; (Chowell et al., 2006b)[2]; (Eichner et al., 2007)[3]; (Nuño et al., 2007a, Gumel et al., 2008)[4]; (Flahault et al., 2006)[5]; (Arino et al., 2008)[6]; (Sattenspiel and Herring, 2003, Nuño et al., 2008)[7]; (Hollingsworth et al., 2006)[8]; (Vardavas et al., 2007)[9]
	5. Stochastic agent-based/individual-based model	AD[1]; ADS[2]; ADSTV[3]; ADSV[4]; ADTV[5]; D[6]; S[7]; V[8]	(Wu et al., 2006)[1]; (Sypsa and Hatzakis, 2009)[2]; (Ferguson et al., 2006)[3]; (Germann et al., 2006, Das et al., 2008, Yasuda and Suzuki, 2009, Tsai et al., 2010)[4]; (Ciofi degli Atti et al., 2008)[5]; (Ohkusa and Sugawara, 2007)[6]; (Lee et al., 2010)[7]; (van den Dool et al., 2008, Basta et al., 2009, Milne et al., 2009, Sypsa et al., 2009, Yang et al., 2009)[8]
	6. Stochastic agent-based/individual-based network model	A[1]; ADSV[2]	(Duerr et al., 2007c)[1]; (Carrat et al., 2006b, Davey and Glass, 2008, Chao et al., 2010)[2];

Table S2: (continued)

Species and spread type	Model type	Interventions	Articles
A. Human-human	7. Stochastic agent-based/individual-based spatially explicit model	ADS	(Ferguson et al., 2005, Halloran et al., 2008)
	8. Stochastic heterogeneous mixing compartmental model	ADSV[1]; ADV[2]; ASV[3]; AV[4]; DS[5]; DV[6]; V[7]	(Glass and Barnes, 2007)[1]; (Rizzo et al., 2008)[2]; (Gojovic et al., 2009)[3]; (Longini et al., 2004)[4]; (Haber et al., 2007)[5]; (Shaban et al., 2009)[6]; (Halloran et al., 2002, Weycker et al., 2005)[7];
	9. Stochastic homogeneous mixing compartmental model	A[1]; T[2]; TV[3]	(Xu et al., 2007)[1]; (Epstein et al., 2007)[2]; (Wood et al., 2007)[3]
	10. Stochastic metapopulation model	AT[1]; T[2]; V[3]	(Colizza et al., 2007)[1]; (Cooper et al., 2006)[2]; (Flahault et al., 2009)[3]
	11. Stochastic network model	D	(Glass et al., 2006, Hsu and Shih, 2010)
	12. Stochastic spatially explicit network model	ADV	(Longini et al., 2005)
B. Bird-bird	1. Deterministic homogeneous mixing compartmental model	D[1]; V[2]	(Elbakidze, 2008)[1]; (Iwami et al., 2009)[2]
	2. Stochastic agent-based/individual-based model	V	(Savill et al., 2006)
	3. Stochastic spatially explicit agent-based/individual-based model	M	(Le Menach et al., 2006)
	4. Stochastic spatially explicit network model	M	(Sharkey et al., 2008)
C. Bird-bird, bird-human and human-human	1. Deterministic metapopulation model	D	(Arino et al., 2007)
D. Animal-animal, animal-human, human-human and human-animal	1. Deterministic multi-host compartmental model	V	(Saenz et al., 2006)

Key: A= antivirals for either or both prophylactic and treatment; D= include workplace closure, contact tracing, quarantine, isolation, cancellation of community and mass gathering, use of personal hygiene and protective equipment; M= movement control and depopulation in animals (including birds); S= school and daycare closure only; T=air travel restriction; V= vaccination before or during the outbreaks. Combination of letters indicates combination of these measures. Where there are more than one set of combination of questions of interests for application of a particular model, superscripts on question of interests correspond to superscripts of respective articles.

Table S3: Summary of natural history parameters of influenza infection in humans either estimated from experimental and observational studies, referenced or assumed for modeling along with list of articles and references.

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
A. Incubation period (day)							
a) Estimated values	1(a). Pandemic influenza A/H1N1 2009	2.0	-	-	-	(Witkop et al., 2010)[1]	-
	1(b). Pandemic influenza A/ H1N1 2009	4.3 (95%CI 2.6-6.0)	4.0	-	-	(Tuite et al., 2010b)[1,2]	-
	2. Seasonal influenza A/H3N2	2.0	-	1.0	3.0	(Canadian Food Inspection Agency)[1,3, 4]	-
b) Referenced values	1. Pandemic influenza A/H1N1 1918	1.0	-	-	-	(Carpenter and Sattenspiel, 2009)[1]	(Longini et al., 2004, Dubé et al., 2008)[1]
	2. Pandemic influenza A/H1N1 2009	2.0 (1.5 – 3.0)	-	1.0	5.0	(Kitching et al., 2006, Boni et al., 2009, Pourbohloul et al., 2009)[1;] (Pourbohloul et al., 2009)[3,4]	(Longini et al., 2004, Ferguson et al., 2005, Longini and Halloran, 2005, Ferguson et al., 2006, Germann et al., 2006, Halloran et al., 2008, Lessler et al., 2009, WHO, 2009)[1]; (WHO, 2009)[3, 4]
	3. Pandemic influenza A/H2N2 1957 and H1N1 2009	2.0	-	1.0	3.0	(Chao et al., 2010)[1,3, 4]	(Canadian Food Inspection Agency, Halloran et al., 2007)[1, 3, 4]

Note: (a) Estimated values are those estimated from empirical data of experimental or observational studies; (b) Referenced values refer to those values taken from other articles or sources; (c) Assumed values are values assumed based on expert opinion or unpublished data sources. Summary estimates are medians and ranges of means, medians, minimum and maximum values of two or more articles. Single value represented value from either one article or same value from two or more articles. Superscript numbers on articles and reference sources correspond to columns of mean =1; median =2; minimum =3; and maximum = 4.

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
b) Referenced values	4. Mutant influenza A/H5N1	1.7 (1.48 – 1.9)	2.0	1.0	3.0	(Ohkusa and Sugawara, 2007)[2,3,4] (Ferguson et al., 2005, Ohkusa and Sugawara, 2007)[1]	(Moser et al., 1979, Longini and Halloran, 2005)[1]; (Longini et al., 2005)[2,3,4]
	5. Pandemic influenza viruses	1.6 (1.0 – 1.9)	2.0	1.0	3.0	(Germann et al., 2006, Colizza et al., 2007, Gardam et al., 2007, Rizzo et al., 2008)[1] (Germann et al., 2006)[2] (Germann et al., 2006, Basta et al., 2009)[3, 4]	(Flahault et al., 1988, Ferguson et al., 2003b, Longini et al., 2004, Ferguson et al., 2005, Gani et al., 2005, Longini and Halloran, 2005)[1]; (Longini et al., 2005)[2] (Canadian Food Inspection Agency, Longini and Halloran, 2005, Halloran et al., 2007)[3, 4]
	6. Novel influenza virus	1.9	-	-	3.0	(Longini et al., 2005)[1] (Grais et al., 2003, Flahault et al., 2006)[4]	(Dubé et al., 2008, Jones et al., 2008)[1]; (OIE, 2007)[4]
	7. Seasonal influenza A/H1N1	-	-	1.0	4.0	(Chen and Liao, 2010) [3, 4]	(Anderson and May, 1991, Thomas and DJ, 2001, Mills et al., 2004)[3, 4]
	8. Seasonal influenza A/H3N2	-	-	1.0	3.5 (3.0 – 4.0)	(Cauchemez et al., 2004, Chen and Liao, 2010) [3, 4]	(Anderson and May, 1991, Nicholson, 1998, Hayden and Aoki, 1999a, Thomas and DJ, 2001, Mills et al., 2004)[3,4]

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
b) Referenced values	9. Influenza viruses	2.4 (1.9 – 2.9)	2.0	1.0	3.0	(Flahault et al., 1994, Tsai et al., 2010)[1] (Chen and Liao, 2010, Tsai et al., 2010)[2,3] (Grais et al., 2004, Chen and Liao, 2010, Tsai et al., 2010)[4]	(Flahault et al., 1988)[1] (Anderson and May, 1991, Thomas and DJ, 2001, Mills et al., 2004, Longini et al., 2005)[2, 3] (Anderson and May, 1991, Thomas and DJ, 2001, Mills et al., 2004, Longini et al., 2005, Office International des Epizooties (OIE), 2007)[4]
c) Assumed values	1. Pandemic influenza A/ H1N1 2009	-	-	1.0	3.0	(Yang et al., 2009)[3, 4]	
	2. Novel influenza virus	2.0	-	-	-	(Arino et al., 2007)1	
B. Latent period (day)							
a) Estimated values	1. Pandemic influenza A/H1N1 2009	2.6 (2.3 – 3.1)	-	-	-	(Tuite et al., 2010b)[1]	
	2. Influenza viruses	1.0	-	-	-	(Canadian Food Inspection Agency)[1]	
b) Referenced values	1. Pandemic influenza A/H1N1 1918	1.9 (1.0 – 3.5)	-	1.15 (0.8 - 1.5)	1.7 (1.5 - 1.9)	(Mills et al., 2004, Chowell et al., 2006a, Chowell et al., 2006b, Chowell et al., 2007a, Chowell et al., 2007b, Massad et al., 2007, Carpenter and Sattenspiel, 2009, Rios-Doria and Chowell, 2009)[1] (Sertsou et al., 2006, Chowell et al., 2008a)[3,4]	(Longini Jr et al., 1978, Longini et al., 2004, Mills et al., 2004, Dubé et al., 2008)[1] (Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005, Ferguson et al., 2006, Wallinga and Lipsitch, 2007) & least-square fitted value to data by (Sertsou et al., 2006)[3]

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
b) Referenced values	2. Pandemic influenza A/H2N2 1957	1.9	-	-	-	(Longini et al., 2004)[1]	(Halloran et al., 2002, Dubé et al., 2008, Jones et al., 2008)[1]
	3. Pandemic influenza A/H1N1 2009	1.5 (1.0 - 3.5)	-	0.9 (0.7 - 1.0)	4.0 (2.9 – 5.0)	(Colizza et al., 2009a, Gojovic et al., 2009, Medlock and Meyers, 2009, Pourbohloul et al., 2009, Sypsa and Hatzakis, 2009, Sypsa et al., 2009, Tuite et al., 2009, Perlroth et al., 2010, Tuite et al., 2010a)[1] (Flahault et al., 2009, Pourbohloul et al., 2009)[3,4]	(Canadian Food Inspection Agency, Longini et al., 2004, Ferguson et al., 2005, Ferguson et al., 2006, Chowell et al., 2008b, Balcan et al., 2009, Boëlle et al., 2009, Flahault et al., 2009, Fraser et al., 2009, Novel Swine-Origin Influenza et al., 2009, Shinde et al., 2009, World Health Organization (WHO), 2009, Tuite et al., 2010b)[1]; (Boëlle et al., 2009, Fraser et al., 2009, World Health Organization (WHO), 2009)[3,4]
	4. Mutant influenza A/H5N1	1.1 (1.0 – 1.2)	1.0	1.0	2.0	(Ohkusa and Sugawara, 2007, Milne et al., 2009)[1,] (Ohkusa and Sugawara, 2007)[2,3, 4]	(Canadian Food Inspection Agency, Longini et al., 2005)[1] (Longini et al., 2005)[2,3,4]

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
b) Referenced values	5. Pandemic influenza viruses	1.5 (0.5 - 1.9)	1.0	1.0 (1.0 - 1.2)	2.0	(Gumel and Moghadas, 2003, Carrat et al., 2006a, Germann et al., 2006, Wu et al., 2006, Colizza et al., 2007, Duerr et al., 2007a, Nuño et al., 2007a, Roberts et al., 2007, Wood et al., 2007, Ajelli and Merler, 2008, Ciofi degli Atti et al., 2008, Tennenbaum, 2008, Balcan et al., 2009, Lunelli et al., 2009, Wein and Atkinson, 2009)[1:] (Germann et al., 2006)[2] (Germann et al., 2006, Roberts et al., 2007, Ajelli and Merler, 2008)[3,4]	(Cauchemez et al., 2004, Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005, Gani et al., 2005, Longini and Halloran, 2005, Longini et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Colizza et al., 2007, Roberts et al., 2007)[1] (Longini et al., 2005)[2] (Ferguson et al., 2005, Longini and Halloran, 2005, Ferguson et al., 2006, Germann et al., 2006, Roberts et al., 2007)[3,4]
	6. Novel influenza virus	1.6 (1.0 – 1.2)	-	1.0	2.0	(Gani et al., 2005, Longini et al., 2005, Hollingsworth et al., 2006, Duerr et al., 2007a, Epstein et al., 2007, Nuño et al., 2008)[1] (Arino et al., 2008)[3,4]	(Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Dubé et al., 2008, Jones et al., 2008)[1]; (Longini et al., 2004)[3,4]
	7. Seasonal influenza A/pandemic influenza A/H1N1 1918	1.3	-	-	-	(Davey et al., 2008)[1]	(Ferguson et al., 2005, Ferguson et al., 2006)[1]
	8. Seasonal influenza A/H1N1	1.9	-	1.0	3.0	(Lessler et al., 2007, Chen and Liao, 2010)[1] (Chen and Liao, 2010)[3,4]	(Anderson and May, 1991, Thomas and DJ, 2001, Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005)[1,3]; (Anderson and May, 1991, Thomas and DJ, 2001, Mills et al., 2004)[3,4]

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
b) Referenced values	9. Seasonal influenza A/H3N2	1.9	-	1.0	3.0	(Chen and Liao, 2010)[1,3,4]	(Anderson and May, 1991, Thomas and DJ, 2001, Mills et al., 2004)[1,3,4]
	10. Influenza viruses	1.9 (0.8 – 1.9)	1.0	1.0	3.0 (2.0 – 3.0)	(Halloran et al., 2002, Weycker et al., 2005, Glass et al., 2006, Duerr et al., 2007a, Eichner et al., 2007, Arino et al., 2008, Brauer, 2008, van den Dool et al., 2008, Chen and Liao, 2010, Tsai et al., 2010)[1] (Tsai et al., 2010)[2] (Halloran et al., 2002, Weycker et al., 2005, Chen and Liao, 2010, Tsai et al., 2010)[3,4]	(Anderson and May, 1991, Thomas and DJ, 2001, Welliver et al., 2001, Hirotsu et al., 2004, Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Wallinga and Lipsitch, 2007, Dubé et al., 2008)[1]; (Longini et al., 2005)[2] (Anderson and May, 1991, Thomas and DJ, 2001, Mills et al., 2004, Longini et al., 2005, Dubé et al., 2008)[3,4]
c) Assumed values	1. Pandemic influenza A/H1N1 2009	2.0	-	1.0	3.0	(Yasuda and Suzuki, 2009)[1];(Yang et al., 2009)[3] (Yang et al., 2009)[4]	-
	2. Mutant influenza A/H5N1	3.0	-	-	-	(Ohkusa and Sugawara, 2009)[1]	-
	3. Novel influenza virus	1.5	-	-	-	(Ferguson et al., 2006)[1]	-
	4. Influenza viruses	1.0	-	-	-	(Hartvigsen et al., 2007)[1]	-
C. Subclinical infectious period (day)							
a) Estimated values	1. Pandemic influenza A/H1N1 1918 (1st wave)	2.9 (95%CI 2.8 -3.1)	-	-	-	(Chowell et al., 2006a)[1]	
	2. Pandemic influenza A/H1N1 1918 (2nd wave)	2.2 (95%CI 1.9-2.7)	-	-	-	(Chowell et al., 2006a)[1]	

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
b) Referenced values	1. Pandemic influenza A/H1N1 2009	1.0 (0.5–2.5)	-	0.0	2.0	(Gojovic et al., 2009, Pourbohloul et al., 2009, Perlroth et al., 2010)[1] (Pourbohloul et al., 2009)[3, 4]	(Longini et al., 2004, Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Boëlle et al., 2009, Flahault et al., 2009, Fraser et al., 2009)[1] (Ferguson et al., 2005, Longini et al., 2005)[3, 4]
	2. Mutant influenza A/H5N1	1.0	-	-	-	(Milne et al., 2009) [1]	(Canadian Food Inspection Agency)
	3. Pandemic influenza viruses	1.0 (0.25 – 4.1)	-	-	-	(Duerr et al., 2007a, Gardam et al., 2007, Tennenbaum, 2008)[1]	(Ferguson et al., 2003b, Longini et al., 2004, Ferguson et al., 2005, Gani et al., 2005, Longini et al., 2005, Germann et al., 2006)[1]
	4. Seasonal influenza A/pandemic influenza A/H1N1 1918	-	-	0.5	0.7	(Davey et al., 2008)[3,4]	(Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Germann et al., 2006)[3,4]
	5. Influenza viruses	3.0 (0.5 - 4.1)	-	-	-	(Glass et al., 2006, Eichner et al., 2007, Brauer, 2008)[1]	(Welliver et al., 2001, Longini et al., 2004)[1]
b) Assumed values	1. Pandemic influenza viruses	0.5	-	-	-	(Wu et al., 2006) [1]	-
D. Clinical infectious period (day)							
a.1) Estimated values (with 95%CI)	1. Pandemic influenza A/H1N1 1918 (1st wave)	1.2 (1.1-1.3)	-	-	-	(Chowell et al., 2006a)[1]	
	2. Pandemic influenza A/H1N1 1918 (2nd wave)	2.6 (2.4–2.8)	-	-	-	(Chowell et al., 2006a) [1]	
	3. Pandemic influenza A/H1N1 2009	3.4 (2.1 – 4.7)	-	-	-	(Tuite et al., 2010b)[1]	
	4. Seasonal influenza A/H1N1	4.5 (3.7-5.3)	-	-	-	(Canadian Food Inspection Agency)[1]	
	5. Seasonal influenza A/H3N2	5.1 (4.5-5.8)	-	-	-	(Canadian Food Inspection Agency)[1]	
	6. Influenza viruses	4.8 (4.3-5.3)	-	-	-	(Canadian Food Inspection Agency)[1]	

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
a.2) Estimated values (without 95%CI)	1. Pandemic influenza A/H1N1 1918	1.8 (1.7 – 3.0)	-	1.7 (1.6 – 1.7)	1.9 (1.8 – 1.9)	(Chowell et al., 2007a, Rios-Doria and Chowell, 2009)[1] (Chowell et al., 2006a)[3]; (Chowell et al., 2007a)[4]	
	2. Pandemic influenza A/H2N2 1957	4.1	-	-	-	(Longini et al., 2004)[1]	
	3. Pandemic influenza A/H1N1 2009	5.6	-	1.0	10.0 (8.0 – 12.0)	(Witkop et al., 2010)[1, 3] (De Serres et al., 2010, Witkop et al., 2010)[4]	
	4. Seasonal influenza A/H3N2	3.8	-	3.1	4.6	(Cauchemez et al., 2004)[1,3,4]	
b) Referenced values	1. Pandemic influenza A/H1N1 1918	4.6 (4.1 – 5.0)	-	2.6 (1.5 – 3.3)	4.2 (2.9 – 7.0)	(Sattenspiel and Herring, 2003, Mills et al., 2004, Chowell et al., 2007b, Massad et al., 2007)[1] (Chowell et al., 2006b, Sertsou et al., 2006, Chowell et al., 2008a, Carpenter and Sattenspiel, 2009)[3, 4]	(Longini Jr et al., 1978, Chin, 2000, Longini et al., 2004, Mills et al., 2004)[1];(Heymann, 2004, Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005, Ferguson et al., 2006, Wallinga and Lipsitch, 2007)[3, 4]

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
b) Referenced values	2. Pandemic influenza A/H1N1 2009	3.8 (2.5 – 7.0)	-	3.8 (1.9 – 4.0)	5.5 (2.9 – 10.0)	(Kitching et al., 2006, Colizza et al., 2009a, Gojovic et al., 2009, Medlock and Meyers, 2009, Pourbohloul et al., 2009, Sypsa and Hatzakis, 2009, Sypsa et al., 2009, Tuite et al., 2009, Perlroth et al., 2010, Tuite et al., 2010a)[1] (Boni et al., 2009, Flahault et al., 2009, Pourbohloul et al., 2009)[3,4]	(Canadian Food Inspection Agency, Longini et al., 2004, Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Chowell et al., 2008b, Halloran et al., 2008, Balcan et al., 2009, Boëlle et al., 2009, Flahault et al., 2009, Fraser et al., 2009, Novel Swine-Origin Influenza et al., 2009, World Health Organization (WHO), 2009, Tuite et al., 2010b)[1]; (Cauchemez et al., 2004, Boëlle et al., 2009, Fraser et al., 2009, World Health Organization (WHO), 2009)[3, 4]
	3. Pandemic influenza A/H2N2 1957/ and H1N1 2009	6.0	-	-	-	(Chao et al., 2010)[1]	(Canadian Food Inspection Agency, Halloran et al., 2007)[1]
	4. Mutant influenza A/H5N1	4.1 (4.0 – 4.1)	-	3.0	6.0	(Ohkusa and Sugawara, 2007, Milne et al., 2009)[1] (Ohkusa and Sugawara, 2007)[3,4]	(Canadian Food Inspection Agency, Longini et al., 2005)[1] (Longini et al., 2005)[1,4]

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
b) Referenced values	5. Pandemic influenza viruses	4.0 (1.8 – 7.0)	-	3.0 (2.5 – 3.0)	8.0 (5.0 – 10.0)	(Gumel and Moghadas, 2003, Carrat et al., 2006a, Germann et al., 2006, Wu et al., 2006, Colizza et al., 2007, Duerr et al., 2007a, Gardam et al., 2007, Nuño et al., 2007a, Roberts et al., 2007, Wood et al., 2007, Ajelli and Merler, 2008, Rizzo et al., 2008, Balcan et al., 2009, Basta et al., 2009, Lunelli et al., 2009, Wein and Atkinson, 2009)[1] (Carrat et al., 2006a, Germann et al., 2006, Tennenbaum, 2008)[3]; (Carrat et al., 2006a, Germann et al., 2006, Ciofi degli Atti et al., 2008, Tennenbaum, 2008) [4]	(Canadian Food Inspection Agency, Flahault et al., 1988, Hayden et al., 1998, Ferguson et al., 2003a, Stiver, 2003, Cauchemez et al., 2004, Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005, Gani et al., 2005, Longini et al., 2005, Bell, 2006, Ferguson et al., 2006, Germann et al., 2006, Colizza et al., 2007, Halloran et al., 2007)[1] (Longini et al., 2004, Mills et al., 2004, Chowell et al., 2006b)[3]; (Cauchemez et al., 2004, Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006) [4]
	6. Seasonal influenza A/pandemic influenza A/H1N1 1918	-	-	3.5	4.1	(Davey et al., 2008)[3, 4]	(Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Germann et al., 2006)[3, 4]

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
b) Referenced values	7. Novel influenza virus	4.0 (1.0 – 7.0)	-	5.0	10 (7.0 – 12.0)	(Grais et al., 2003, Gani et al., 2005, Longini et al., 2005, Flahault et al., 2006, Hollingsworth et al., 2006, Saenz et al., 2006, Duerr et al., 2007b, Nuño et al., 2007b, Nuño et al., 2008)[1] (Grais et al., 2003, Epstein et al., 2007, Nuño et al., 2007b)[4]	(Couch and Kasel, 1983, Rvachev L and IM., 1985, Stiver, 2003, Longini et al., 2004, Stöhr, 2004, Ferguson et al., 2005, Longini et al., 2005, Centers for Disease Control and Prevention (CDC), 2006, Dubé et al., 2008, Jones et al., 2008)[1]; (Couch et al., 1986, Centers for Disease Control and Prevention (CDC), 2006)[3]; (Couch and Kasel, 1983, Rvachev L and IM., 1985, Longini et al., 2004, Ferguson et al., 2005, Centers for Disease Control and Prevention (CDC), 2006, Ferguson et al., 2006, Germann et al., 2006)[4]
	8. Seasonal influenza A/H1N1	4.1	-	2.0	8.0	(Lessler et al., 2007, Chen and Liao, 2010)[1,] (Chen and Liao, 2010)[3,4]	(Anderson and May, 1991, Thomas and DJ, 2001, Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005)[1]; (Anderson and May, 1991, Thomas and DJ, 2001, Mills et al., 2004)[3, 4]

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
b) Referenced values	9. Seasonal influenza A/H3N2	4.1 (3.8 – 4.1)	-	2.0	8.0	(Addy et al., 1991, Cauchemez et al., 2008, Chen and Liao, 2010)[1]; (Chen and Liao, 2010)[3,4]	(Anderson and May, 1991, Thomas and DJ, 2001, Cauchemez et al., 2004, Mills et al., 2004, Dubé et al., 2008)[1]; (Anderson and May, 1991, Thomas and DJ, 2001, Mills et al., 2004)[3,4]
	10. Seasonal influenza A/H3N2/ influenza B	3.8	-	-	-	(Cauchemez et al., 2008)[1]	(Cauchemez et al., 2004)[1]
	11. Influenza viruses	4.1 (1.4 – 7.0)	-	3.0 (2.0 – 3.0)	6.0 (6.0 – 10.0)	(Flahault et al., 1994, Halloran et al., 2002, Grais et al., 2004, Lavenu et al., 2004, Weycker et al., 2005, Glass et al., 2006, Eichner et al., 2007, Arino et al., 2008, Brauer, 2008, Chowell et al., 2008b, van den Dool et al., 2008, Shaban et al., 2009, Tuite et al., 2009, Chen and Liao, 2010, Tsai et al., 2010)[1] (Halloran et al., 2002, Weycker et al., 2005, Chen and Liao, 2010, Tsai et al., 2010)[3,4]	(Rvachev L and IM., 1985, Flahault et al., 1988, Anderson and May, 1991, Thomas and DJ, 2001, Welliver et al., 2001, Hirotsu et al., 2004, Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Fraser, 2007, Wallinga and Lipsitch, 2007, Chowell et al., 2008b, Chowell and Nishiura, 2008, Dubé et al., 2008, Tuite et al., 2010b)[1]; (Rvachev L and IM., 1985, Anderson and May, 1991, Thomas and DJ, 2001, Mills et al., 2004, Longini et al., 2005, Dubé et al., 2008)[3,4]

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
c) Assumed values	1. Pandemic influenza A/H2N2 1957	-	-	3.8	5.3	(Arinaminpathy and McLean, 2009)[3,4]	
	2. Pandemic influenza A/H3N2 1968	3.0	-	-	-	(Cooper et al., 2006)[1]	
	3. Pandemic influenza A/H1N1 2009	4.0 (3.0 – 5.0)	-	3.0	7.0	(Yang et al., 2009, Yasuda and Suzuki, 2009)[1];(Yang et al., 2009)[3,4]	
	4. Pandemic influenza viruses	-	-	2.0	3.0	(Nigmatulina and Larson, 2009)[3,4]	
	5. Novel influenza virus	4.0	-	-	-	(Arino et al., 2007)[1]	
	6. Influenza viruses	3.0	-	-	-	(Hartvigsen et al., 2007, Vardavas et al., 2007)[1]	
E. Immune period (day)		All modeling articles assumed immunity last till the duration of simulation after vaccination or recovery					
F. Percentage of pre-existing immunity (%)							
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	-	4.0	34.0	(Hancock et al., 2009)[3, 4]	
b) Referenced values	1. Pandemic influenza A/H1N1 1918	-	50.0	-	-	(Rios-Doria and Chowell, 2009)[2]	(Barry et al., 2008)[2];
	2. Pandemic influenza A/H1N1 2009	-	34.0 (5.0 – 50.0)	30.0	50.0 (15.0 – 70.0)	(Kitching et al., 2006, Gojovic et al., 2009, Tuite et al., 2010a)[2] (Tuite et al., 2010a)[3] (Gojovic et al., 2009, Tuite et al., 2009, Tuite et al., 2010a)[4]	(Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC), 2009, Coburn et al., 2009, Fisman et al., 2009, Flahault et al., 2009, Fraser et al., 2009)[2]; (Centers for Disease Control and Prevention (CDC), 2009, Fisman et al., 2009)[3]; (Hirotsu et al., 2004, Wallinga and Lipsitch, 2007, Centers for Disease Control and Prevention (CDC), 2009, Coburn et al., 2009, Fisman et al., 2009, Flahault et al., 2009, Fraser et al., 2009)[4]

Table S3: (continued)

Disease states	Agent	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Reference sources
b) Referenced values	3. Mutant influenza A/H5N1	-	-	-	27.0	(Ferguson et al., 2005)[4]	(Fox et al., 1982) [4]
	4. Novel influenza virus	-	30.0	-	100.0	(Nuño et al., 2007b)[2,4]	(Castillo-Chavez et al., 1989)[2,4]
	5. Seasonal influenza A/H3N2	-	-	-	27.0	(Cauchemez et al., 2008) [3]	(Longini et al., 1988) [4]
	6. Influenza viruses	-	-	-	30.0	(van den Dool et al., 2008) [3,4]	(Hirotsu et al., 2004, Wallinga and Lipsitch, 2007)[3, 4]
c) Assumed values	1. Pandemic influenza A/H1N1 1918	-	-	10.0	20.0	(Sertsou et al., 2006)[3,4]	-
	2. Novel influenza virus	-	25.0	-	-	(Flahault et al., 2006)[2]	-
	3. Influenza viruses	-	-	-	62.5 (50.0 – 75.0)	(Flahault et al., 1994, Lavenu et al., 2004)[4]	-

Table S4: Summary of natural history parameters of influenza infection in animals either estimated from experimental and observational studies, or referenced or assumed for modeling along with list of articles and references.

Disease states	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	Reference sources
A. Incubation period (day)	Swine species					
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	1.0 (1.0–2.0)	2.5 (1.0 – 3.0)	(Howden et al., 2009, Lange et al., 2009, Brookes et al., 2010)[2,3]	-
B. Latent period (day)						
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	1.0	2.0 (2.0 – 5.0)	(Lange et al., 2009, Brookes et al., 2010, Vincent et al., 2010)[2,3]	-
	2. Swine influenza A/ H1N1	-	1.0	2.0	(Vincent et al., 2009)[2,3]	
C. Clinical infectious period (day)						
a) Estimated values	1. Pandemic influenza A/H1N1 2009 (individual animal level)	-	7.0 (3.0 – 7.0)	8.0 (5.0 – 15.0)	(Lange et al., 2009, Brookes et al., 2010, Vincent et al., 2010)[2,3]	
	2. Pandemic influenza A/H1N1 2009 (herd-level)	-	10.0	31 (20.0 – 42.0)	(Pasma and Joseph, 2010)[2] (Howden et al., 2009, Pasma and Joseph, 2010)[3]	
	3. Swine influenza A/H1N1	-	3.0	5.0	(Vincent et al., 2009)[2,3]	
b) Referenced values	1. Novel influenza virus	7.0	-	-	(Saenz et al., 2006)[1]	(Hinshaw et al., 1981, Brown, 2000, Ortiz-Pelaez et al., 2006)[1]
D. Immune period (day)						
a) Estimated values	1. Swine influenza viruses	-	365.0	692.5 (545.0 – 840.0)	(Blaskovic et al., 1970)[2] (Blaskovic et al., 1970, Desrosiers et al., 2004)[3]	

Note: (a) Estimated values are those estimated from empirical data of experimental or observational studies; (b) Referenced values refer to those values taken from other articles or sources; (c) Assumed values are values assumed based on expert opinion or unpublished data sources. Summary estimates are medians and ranges of means, medians, minimum and maximum values of two or more articles. Single value represented value from either one article or same value from two or more articles. Superscript numbers on articles and reference sources correspond to columns of mean =1; minimum =2; and maximum = 3.

Table S5: Summary of natural history parameters of avian influenza infection in birds used for modeling.

Disease states	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	List of articles	Reference sources
A. Incubation period (day)						
b) Referenced values	1. Avian influenza A/H5N1(individual level)	5.0	-	-	(Elbakidze, 2008)[1]	(Mannelli et al., 2007)[1]
c) Assumed values	1. Avian influenza A/H7N1(individual level)	-	2.0	6.0	(Ward et al., 2009)[2,3]	-
	2. Avian influenza A/H7N7(individual level)	-	1.0	3.0	(Stegeman et al., 2004)[2,3]	-
B. Latent period (day)						
b) Referenced values	1. Avian influenza A/ H5N1 (individual level)	1.8 (1.5 – 2.0)	1.0	2.0	(Savill et al., 2006, Sharkey et al., 2008)[1]; (Tiensin et al., 2007, Sharkey et al., 2008)[2,3]	(van der Goot et al., 2003, Swayne and Beck, 2005, Tian et al., 2005, Gao et al., 2006)[1];(van der Goot et al., 2003, Lee et al., 2005, Swayne and Beck, 2005, Tian et al., 2005, Gao et al., 2006, Swayne et al., 2006, Webster et al., 2006)[2,3]
	2. Avian influenza A/H7N7(individual level)	2.0	-	-	(Le Menach et al., 2006, Bos et al., 2007, Bavinck et al., 2009)[1]	(European, 2003, Savill et al., 2006, van der Goot et al., 2007)[1]
c) Assumed value	1. Avian influenza A/H7N7(individual level)	2.0	-	-	(van der Goot et al., 2005) [1]	-
C. Subclinical infectious period (day)						
b) Referenced values	1. Avian influenza A/H5N1(individual level)	1.0	-	-	(Savill et al., 2006)[1]	(Dube et al., 2011)[1]
	2. Avian influenza A/H7N7(individual level)	4.0	-	6.0	(Le Menach et al., 2006)[1, 3]	(European, 2003, Stegeman et al., 2004)[1, 3]
D. Clinical infectious period (day)						
a.1) Estimated values (with 95%CI)	1. Highly pathogenic avian influenza A/H5N2	6.8 (4.91 – 8.7)	-	-	(van der Goot et al., 2003)[1]	
	2. Low pathogenic avian influenza A/H5N2	4.3 (2.6 – 5.9)	-	-	(van der Goot et al., 2003)[1]	
	3. Avian influenza A/H7N7	6.3 (3.9 – 8.7)			(van der Goot et al., 2005)[1]	
b) Referenced values	1. Avian influenza A/ H5N1	2.8 (1.5 – 4.0)	1.0	3.5 (3.0 – 4.0)	(Savill et al., 2006, Sharkey et al., 2008)[1]; (Tiensin et al., 2007, Sharkey et al., 2008) [2,3]	(Anonymous, 2007, Dube et al., 2011)[1]; (Lee et al., 2005, Tian et al., 2005, Swayne et al., 2006, Webster et al., 2006, Anonymous, 2007)[2,3]

Table S5: (continued)

Disease states	Agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	List of articles	Reference sources
b) Referenced values	2. Avian influenza A/ H5N1 (Flock level)	10.0	-	-	(Elbakidze, 2008)[1]	(Office International des Epizooties (OIE), 2007)[1]
	3. Avian influenza A/H7N7	13.8	1.0	6.0	(Bos et al., 2007)[1] (Le Menach et al., 2006)[2,3]	(van der Goot et al., 2005)[1]; (European, 2003, Sanco, 2003, van der Goot et al., 2003, Stegeman et al., 2004)[2,3]
	4. Avian influenza A/H7N7 (Flock level)	6.3	4.0	12.0	(Iwami et al., 2009)[1]; (Bavinck et al., 2009)[2,3]	(Capua and Alexander, 2004, Stegeman et al., 2004)[1]; (Stegeman et al., 2004)[2,3]
	5. Low pathogenic avian influenza	9.2 (4.3 -14.0)	-	-	(Guberti et al., 2007)[1]	(Grenfell and Anderson, 1985, Aznar et al., 2011)[1]
c) Assumed values	1. Avian influenza A/ H5N1 (Village level)	7.0			(Ward et al., 2009)[1]	

Note: (a) Estimated values are those estimated from empirical data of experimental or observational studies; (b) Referenced values refer to those values taken from other articles or sources; (c) Assumed values are values assumed based on expert opinion or unpublished data sources. Summary estimates are medians and ranges of means, medians, minimum and maximum values of two or more articles. Single value represented value from either one article or same value from two or more articles. Superscript numbers on articles and reference sources correspond to columns of mean =1; minimum =2; and maximum = 3.

Table S6: Distributions of natural history of influenza infection in human and bird populations either estimated from experimental and observational studies, referenced or assumed for modeling along with list of articles and references.

Disease states	Agent	Distributions used	Article
Human			
1. Incubation period			
a) Estimated values	1. Pandemic influenza A/H1N1 2009	Log-normal with a mean duration of 4.3 (95%CI 2.6–6.6)	(Tuite et al., 2010b)
b) Referenced/assumed values	1. Pandemic H2N2 1957/H1N1 2009	Mean of 1.9 days with empirical distribution of 1 day (30%); 2 days (50%); 3 days (20%)	(Chao et al., 2010)
	2. Pandemic influenza A/H1N1 2009	(Exponential with a mean of 1.4 day)[1]; (Uniform with a range of 1–3 days)[2]	(Boni et al., 2009)[1]; (Yang et al., 2009)[2]
	3. Mutant avian influenza A/H5N1	Mean of 1.9 days with empirical distribution of 1 day (30%); 2 days (50%); 3 days (20%)	(Ohkusa and Sugawara, 2007)
	4. Pandemic influenza virus	Mean of 1.9 days and empirical distribution of 1 day (30%); 2 days (50%); 3 days (20%)	(Longini et al., 2004, Longini et al., 2005, Germann et al., 2006, Colizza et al., 2007)
	5. Novel influenza virus	Gamma with a mean of 1.9 days and coefficient of variation of 37.8%	(Duerr et al., 2007a)
	6. Influenza viruses	(Right-shifted Weibull with a fixed offset of 0.5 days, shape parameter of 2.21 (95% CI 1.36–3.37) and scale parameter of 1.10 (95% CI 0.83–1.42) giving a mean incubation period of 1.48 days and standard deviation of 0.47 days)[1]; (Mean of 1.9 days with empirical distribution of 1 day (30%); 2 days (50%); 3 days (20%))[2]	(Ferguson et al., 2005)[1]; (Tsai et al., 2010)[2]
2. Latent period			
a) Estimated values	1. Mutant influenza A/H5N1	Right-shifted Weibull with a fixed offset of 0.5 days (lower bound cut-off value), shape parameter of 2.24 and scale parameter of 1.11	(Ferguson et al., 2005)
b) Referenced/assumed values	1. Pandemic influenza A/H1N1 2009	Exponential with a mean of 1.25 days with an offset of 0.75 day (lower bound cut-off value)	(Perlroth et al., 2010)
	2. Mutant influenza A/H5N1	Mean of 1.9 days and empirical distribution of 1 day (30%), 2 days (50%) and 3 days (20%)	(Longini et al., 2004, Longini et al., 2005, Ohkusa and Sugawara, 2007)

Note: In cases where more than one distribution was used for a particular influenza strain, superscript numbers on distributions corresponds to those on the respective articles.

Table S6: (continued)

Disease states	Agent	Distributions used	Article
b) Referenced/assumed values	3. Pandemic influenza virus	(Exponential with a mean of 1.2 days with an offset of 0.75 day)[1]; (Exponential with a mean of 1.4 days)[2]; (Right-shifted Weibull with a fixed offset of 0.5 day (lower bound cut-off value), shape parameter of 2.24 and scale parameter of 1.11)[3]; (Weibull with a fixed offset of 0.5 day (lower bound cut-off value), shape parameter of 2.21 and variable scale parameter values selected based on the serial intervals (which in turn were randomly selected from a range between latent and infectious periods; 1.6–10 days)[4]; (Mean of 1.9 days with empirical distribution of 1 day (30%), 2 days (50%), 3 days(20%))[5]	(Colizza et al., 2007)[1]; (van den Dool et al., 2008)[2]; (Wu et al., 2006)[3]; (Lessler et al., 2007)[4]; (Germann et al., 2006)[5]
	4. Seasonal influenza virus A & H1N1 2009	Exponential with a mean of 1.25 days with an offset of 0.75 day (lower bound cut-off value)	(Davey et al., 2008)
3. Clinical infectious period			
b) Referenced/assumed values	1. Pandemic influenza A/ H1N1 1918	Exponential with a mean of 3 days	(Davey and Glass, 2008)
	2. Pandemic influenza A/H1N1 2009	(Exponential with mean of 3 days)[1]; (Gamma with mean varied from 3.8–5.5 days)[2]; (Log-normal with a mean of 9.3 days and 95%CI 2.6–24.2)[3]; (Uniform with a range 3–7 days)[4].	(Perlroth et al., 2010)[1]; (Boni et al., 2009)[2]; (Tuite et al., 2010b)[3]; (Yang et al., 2009)[4]
	3. Mutant avian influenza A/H5N1	Mean of 4.1 days and empirical distribution of 3 days (30%), 4 days (40%), 5 days (20%), and 6 days (10%).	(Halloran et al., 2002, Longini et al., 2004, Longini et al., 2005, Weycker et al., 2005, Ohkusa and Sugawara, 2007)
	4. Pandemic influenza virus	(Exponential with a mean of 3 days)[1]; (Log-normal with mean of log(-0.72 days and 95%CI -1.64– -0.09 days) and standard deviation of log(1.8 days with 95%CI 1.3–2.5 days))[2]; (Mean of 4.1 days and empirical distribution of 3 days (30%), 4 days (40%), 5 days (20%), 6 days (10%))[3].	(Colizza et al., 2007)[1]; (Ferguson et al., 2005, Ciofi degli Atti et al., 2008)[2]; (Germann et al., 2006)[3]
	5. Novel influenza viruses	Gamma with a mean of 5 days and coefficient of variation of 33.3%.	(Duerr et al., 2007a)
	6. Seasonal influenza A/H1N1	Log-normal with variable median values selected based on serial intervals (which in turn were randomly selected from a range between latent and infectious periods; 1.6–10 days) and a variance of 0.23.	(Lessler et al., 2007)
	7. Seasonal influenza A/H3N2	(Gama with a mean of 3.8 days and standard deviation of 2 days, and infectious period truncated at 10 days)[1]; (Gamma with scale parameter of 2 and shape parameter of 2.05)[2]	(Cauchemez et al., 2008)[1]; (Addy et al., 1991)[2]

Table S6: (continued)

Disease states	Agent	Distributions used	Article
b) Referenced/assumed values	8. Influenza viruses	(Exponential with mean of 3 days)[1]; (Exponential with a mean of 1.4 days)[2]; (Mean of 4.1 days and empirical distribution of 3 days (30%), 4 days (40%), 5 days (20%), 6 days (10%))[3]	(Glass et al., 2006)[1]; (van den Dool et al., 2008)[2]; (Halloran et al., 2002, Weycker et al., 2005, Tsai et al., 2010)[3];
B. Bird			
1. Latent period			
b) Referenced/assumed values	1. Avian influenza A/H5N1	(Latent period of 48 hours + Binomial(48, 0.25) where p = probability of remaining in the latent period)1; (Normal with a mean of 1.5 days and standard deviation of 1 day)[2]	(Savill et al., 2006)[1]; (Sharkey et al., 2008)[2];
	2. Avian influenza A/H7N7	Gama with a mean of 0.5 per day and shape parameter of 20	(Bos et al., 2007)
2. Subclinical infectious period			
b) Referenced/assumed values	1. Avian influenza A/H5N1	Subclinical infectious period of 24 hours + Binomial(24, 0.25) where p = probability of remaining in this state.	(Savill et al., 2006)
3. Clinical infectious period			
b) Referenced/assumed values	1. Avian influenza A/H5N1	Binomial(96, 0.05) where p = probability of remaining in this state.	(Savill et al., 2006)
	2. Avian influenza A/H7N7	(Gamma with a mean of 0.159 per day with a shape parameter of 20)[1]; (Exponential around a mean of 6.3 days with 95% CI 3.9–8.7 days)[2]	(Bos et al., 2007)[1]; (van der Goot et al., 2005) [2]

Table S7: Summary of daily contact frequencies in human and animal populations either estimated from experimental and observational studies, or referenced or assumed for modeling along with list of articles and references.

Species	Contacts category	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	Reference sources
1. Humans-humans	**A. Age**				(Hens et al., 2009)[1]	
a) Estimated values	1. <5	10.21 (7.65)	-	-		
	2. 5-9	14.81 (10.09)	-	-		
	3. 10–14	18.69 (13.4)	-	-		
	4. 15–19	19.93 (21.14)	-	-		
	5. 20–29	17.18 (25.72)	-	-		
	6. 30–39	17.83 (21.68)	-	-		
	7. 40–49	17.51 (23.29)	-	-		
	8. 50–59	15.96 (20.84)	-	-		
	9. 60–69	10.51 (14.47)	-	-		
	10. 70+	7.71 (10.97)	-	-		
	B. Household				(Hens et al., 2009) [1]	
	1. Household size 1	11.23 (18.26)	-	-		
	2. Household size 2	13.32 (17.89)	-	-		
	3. Household size 3	14.67 (16.44)	-	-		
	4. Household size 4	17.71 (17.67)	-	-		
	5. Household size 5	19.49 (29.12)	-	-		
	6. Household size 6+	19.3 (13.14)	-	-		
	C. Students				(Mikolajczyk et al., 2008) [1]	
	1. Students -classmates	38.4	-	-		
	2. Students –non-classmates	14.8	-	-		
b) Referenced values	**A. Activity based**				(Nigmatulina and Larson, 2009) [1]	(Fu, 2005, Wallinga et al., 2006, Fu, 2007) [1]
	1. Low activity	2.0	-	-		
	2. Medium activity	10.0	-	-		
	3. High activity	50.0	-	-		
	Age group				(Davey and Glass, 2008) [1]	(Glass and Glass, 2008) [1]
	1. Children (0–11 years)	14.0 (3.0–24.0)	-	-		
	2. Teen (12–18 years)	4.0 (3.0–4.0)	-	-		
	3. Adult (19–64 years)	6.0 (3.0 – 13.0)	-	-		
	4. Senior (65+ years)	4.0 (3.0 – 5.0)	-	-		

Table S7: (continued)

Species	Contacts category	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	Reference sources
b) Referenced values	**Community structure**					
	1. Community in general	16.0 (1.0–32.0)	5.0 (5.0 – 14.0)	27.0 (24.0–50.0)	(Duerr et al., 2007a, Eichner et al., 2007, Larson, 2007, Gojovic et al., 2009)[1,2,3]	(Wallinga et al., 2006) and calibrated [1,2,3]
	2. Health care worker with coworkers	2.0 (2.0–8.0)	-	-	(Kitching et al., 2006, Lee et al., 2009b) [1]	Pilot studies done by MIDA[1]
	3. Health care worker with patients	30.0	-	-	(Kitching et al., 2006, Lee et al., 2009b) [1]	Pilot studies done by MIDA[1]
	4. Student with classmates	14.0 (14.0–15.0)	-	-	(Kitching et al., 2006, Lee et al., 2009b) [1]	Pilot studies done by MIDA[1]
	5. Student with non-classmates	15.0	-	-	(Kitching et al., 2006, Lee et al., 2009b) [1]	Pilot studies done by MIDA[1]
c) Assumed values	**A. Age group**					
	1. Children (0-11 years)	6.0	-	-	(Glass et al., 2006) [1]	
	B. Community structure					
	1. Community in general	1.0 (1.0–2.0)	-	1.0	(Flahault et al., 1994, Glass et al., 2006) [1]	
2. Bird - bird						
a) Estimated values	1. Maximum farms visited by feed lorry/trip	-	-	6.0	(Sharkey et al., 2008) [1]	
b) Referenced values	1. Flock to flock contact rate/day	-	0.2	0.3	(Elbakidze, 2008) [1]	(Office International des Epizooties (OIE), 2007) [1]
c) Assumed values	1. Inter-company contact /day	3.0	-	-	(Sharkey et al., 2008) [1]	
	2. Maximum farms visited by slaughter lorry/day	-	-	4.0	(Sharkey et al., 2008) [1]	

Note: (a) Estimated values are those estimated from empirical data of experimental or observational studies; (b) Referenced values refer to those values taken from other articles or sources; (c) Assumed values are values assumed based on expert opinion or unpublished data sources. Summary estimates are medians and ranges of means, medians, minimum and maximum values of two or more articles. Single value represented value from either one article or same value from two or more articles. Superscript numbers on articles and reference sources correspond to columns of mean =1; minimum =2; and maximum = 3.

Table S8: Summary of transmission probability per contact of influenza viruses' infection in human and bird populations estimated, referenced or assumed for modeling.

Transmission parameter	Spread in species and agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	Reference sources
A. Human-human (all contact types combined)						
a) Estimated values	1. Pandemic influenza A/H1N1 1918	0.51	-	-	(Duerr et al., 2007a, Massad et al., 2007, Nuño et al., 2007b)[1]	
	2. Novel influenza viruses	0.24 (0.1–0.024)	-	-	(Longini and Halloran, 2005, Germann et al., 2006, Ohkusa and Sugawara, 2007) [1]	
	3. Influenza viruses	0.24	0.39	0.78	(Tsai et al., 2010)[1]; (van den Dool et al., 2008)[2,3]	
b) Referenced values	1. Pandemic influenza A/H1N1 2009	0.0435 (0.00255–0.6)	-	-	(Kitching et al., 2006, Lee et al., 2009b) [1]	(Longini et al., 2004, Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Halloran et al., 2008) [1]
	2. Novel influenza viruses	-	0.55 (0.5–0.6)	0.7	(Duerr et al., 2007a, Nuño et al., 2007b)[2,3]	
	3. Influenza viruses	-	0.2503 (0.0006-0.5)	0.0012	(Eichner et al., 2007, Xu et al., 2007) [1]	(Stilianakis et al., 1998) [1]
B. Bird-bird						
c) Assumed values	1. Avian influenza A/H5N1(within flock/day)	0.5	-	-	(Sharkey et al., 2008) [1]	
	2. Avian influenza A/H5N1(per dangerous slaughterhouse contact)	0.25	-	-	(Sharkey et al., 2008) [1]	

Note: (a) Estimated values are those estimated from empirical data of experimental or observational studies; (b) Referenced values refer to those values taken from other articles or sources; (c) Assumed values are values assumed based on expert opinion or unpublished data sources. Summary estimates are medians and ranges of means, medians, minimum and maximum values of two or more articles. Single value represented value from either one article or same value from two or more articles. Superscript numbers on articles and reference sources correspond to columns of mean =1; minimum =2; and maximum = 3.

Table S9: Summary of transmission coefficients/rates of influenza viruses infection in human and animal populations either estimated from experimental and observational studies, referenced or assumed for modeling along with list of articles and references

Transmission parameter	Spread in species and agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	Reference sources
I. Transmission coefficient/rate - per day						
A. Human-human (all contact types combined)						
a) Estimated values	1. Pandemic influenza A/H1N1 2009	0.060192 (0.0095–0.060192)	0.00001	0.6	(Sypsa and Hatzakis, 2009, Sypsa et al., 2009)[1,2,3]	
	2. Novel influenza viruses	0.00058	0.00029	0.00102	(Haber et al., 2007)[1,2,3]	
	3. Influenza viruses	-	0.000005	0.08	(Halloran et al., 2002)[1,2,3]	
b) Referenced values	1. Pandemic influenza A/ H2N2 1957	0.0125 (0.00001–0.08)	-	-	(Longini et al., 2004) [1]	(Longini, 1988, Addy et al., 1991) [1]
c) Assumed values	1. Novel influenza viruses	-	0.58	0.64	(Carrat et al., 2006a)[2,3]	
B. Bird - Bird						
a) Estimated values	1. Avian influenza A/H5N1 (bird level)	2.66	2.01	2.55	(Tiensin et al., 2007)[1,2,3]	
	2. Avian influenza A/H5N1 (flock level)	0.66	0.5	0.87	(Tiensin et al., 2007)[1,2,3]	
	3. Avian influenza A/H5N2 (bird level)	0.24	0.12	0.45	(van der Goot et al., 2003#1502)[1,2,3]	
	4. Avian influenza A/H7N7 (bird level)	33	-		(van der Goot et al., 2005) [1]	
	5. Avian influenza viruses	0.22	-	0.42	(van der Goot et al., 2003)[1,3]	
C. Zoonotic spread						
c) Assumed values	1. Novel influenza virus					
	a) Bird – human	0.012	-	-	(Arino et al., 2007) [1]	
	b) Human - human	0.03	-	-	(Arino et al., 2007) [1]	

Note: (a) Estimated values are those estimated from empirical data of experimental or observational studies; (b) Referenced values refer to those values taken from other articles or sources; (c) Assumed values are values assumed based on expert opinion or unpublished data sources. Summary estimates are medians and ranges of means, medians, minimum and maximum values of two or more articles. Single value represented value from either one article or same value from two or more articles. Superscript numbers on articles and reference sources correspond to columns of mean =1; minimum =2; and maximum = 3. Column for median estimates for transmission coefficient are excluded since there is no estimate available.

Table S9: (continued)

Transmission parameter	Spread in species and agent	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	Reference sources
II. Transmission coefficient/rate - continuous time						
A. Human-human (all contact types combined)						
a) Estimated values	1. Pandemic influenza A/H1N1 2009	-	0.00001	0.0125	(Yasuda and Suzuki, 2009)[2,3]	
	2. Influenza viruses	0.581	0.199	0.425	(Arino et al., 2008)[1;] (Shaban et al., 2009)[2,3]	
b) Referenced values	1. Novel influenza virus	0.00017			(Hsu and Shih, 2010) [1]	(Ferguson et al., 2005) [1]
C. Zoonotic spread						
1. Between bird-human						
c) Assumed values	1. Novel influenza virus					
	a) Bird–bird	0.15 (0.1–0.2)	-	-	(Iwami et al., 2007, Kim et al., 2010) [1]	
	b) Human – human	0.0006	0.0015	0.0025 (0.002–0.003)	(Kim et al., 2010)[1]; (Iwami et al., 2007)[2]; (Iwami et al., 2007, Kim et al., 2010)[3]	
2. Between animal -human						
c) Assumed values	1. Novel influenza virus				(Saenz et al., 2006) [1]	
	a) Swine-swine	0.2857	-	-		
	b) Swine-human	0.00123				
	c) Human-human	0.3	-	-		
	d) Human-swine	0.122851	-	-		

Table S10: Summary of R_0 and generation intervals of influenza viruses infection in human and animal populations estimated from experimental and observational studies referenced or assumed for modeling along with list of articles and references.

Disease transmission parameters	**Spread type and agent**	**Subject of interest**	**Median of means (Range)**	**Median of medians (Range)**	**Median of min. values (Range)**	**Median of max. values (Range)**	**Article**	**Source Reference sources**
1. Basic reproductive ratio (R_0)	**A. Humans - humans**							
a.1) Estimated values (with 95%CI)	1(a). Pandemic influenza A/H1N1 1918 (using first 10 days outbreak data of spring wave of Geneva, Switzerland)	Individual	1.6 (1.5 – 1.7)	-	-	-	(Chowell et al., 2007a)[1]	
	1(b). Pandemic influenza A/H1N1 1918 (using first 10 days outbreak data of autumn wave of Geneva, Switzerland)	Individual	3.1 (2.8 – 1.7)	-	-	-	(Chowell et al., 2007a) [1]	
	1(c). Pandemic influenza A/H1N1 1918 (using non-hospitalized and asymptomatic cases outbreak data of 1st phase/spring wave in Geneva, Switzerland)	Individual	1.49 (1.45 – 1.53)	-	-	-	(Chowell et al., 2006a) [1]	
	1(d). Pandemic influenza A/H1N1 1918 (using non-hospitalized and asymptomatic cases data of 2nd phase/autumn wave of Geneva, Switzerland)	Individual	3.8 (3.6 – 3.9)	-	-	-	(Chowell et al., 2006a) [1]	

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
	1(e). Pandemic influenza A/H1N1 1918 (using early exponential growth phase of autumn wave daily case notification data of San Francisco, California)	Individual	3.0 (2.7 – 3.3)	-	-	-	(Chowell et al., 2007b) [1]	
	1(f). Pandemic influenza A/H1N1 1918 (using deterministic SIR compartmental model of daily case notification data of autumn wave of San Francisco, California)	Individual	2.4 (2.2 – 2.6)	-	-	-	(Chowell et al., 2007b) [1]	
a.1) Estimated values (with 95%CI)	1(g). Pandemic influenza A/H1N1 1918 (using complex SEIR model of daily case notification data of autumn wave of San Francisco, California)	Individual	2.2 (1.6 – 2.1)	-	-	-	(Chowell et al., 2007b) [1]	
	1(h). Pandemic influenza A/H1N1 1918 (using SIR Bayesian approach method of daily case notification data of autumn wave San Francisco, California)	Individual	2.1 (1.1 – 3.0)	-	-	-	(Chowell et al., 2007b) [1]	
	1(i). Pandemic influenza A/H1N1 1918	Individual	-	2.0 (1.7 – 2.3)	-	-	(Mills et al., 2004) [1]	
	2(a). Pandemic influenza A/H1N1 2009	Individual	1.3 (1.3 – 1.4)	-	-	-	(Tuite et al., 2010b) [1]	
	2(b). Pandemic influenza A/H1N1 2009	Individual	1.4 (1.4 – 1.5)	-	-	-	(Pourbohloul et al., 2009) [1]	

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
a.1) Estimated values (with 95%CI)	2(c). Pandemic influenza A/H1N1 2009 (using intrinsic growth rate and generation interval obtained from household studies)	Individual	2.2 (2.1 – 2.4)	-	-	-	(Boëlle et al., 2009) [1]	
	2(d). Pandemic influenza A/H1N1 2009 (using intrinsic growth rate and generation interval obtained from viral excretion of experimental influenza infection study)	Individual	2.6 (2.4 – 2.8)	-	-	-	(Boëlle et al., 2009) [1]	
	2(e). Pandemic influenza A/H1N1 2009 (using intrinsic growth rate and generation interval obtained from hypothetical distribution from Elveback et al., (2008))	Individual	3.1 (2.9 – 3.5)	-	-	-	(Boëlle et al., 2009) [1]	
	2(f). Pandemic influenza A/H1N1 2009 (using real time estimation of averaging the number of secondary cases across all possible chains of transmissions of epidemic curve)	Individual	-	3.2 (2.1 – 4.0)	-	-	(Boëlle et al., 2009) [1]	
	3. Seasonal influenza A/H1N1	Individual	-	1.19 (0.76 – 1.86)	-	-	(Chen and Liao, 2010)[2]	
	4. Seasonal influenza A/H3N2	Individual	-	1.41 (0.92 – 2.19)	-	-	(Chen and Liao, 2010)[2]	
	5. Seasonal influenza viruses	Individual	1.3 (1.2 – 1.4)	-	-	-	(Chowell et al., 2008b)[1]	

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
a.2) Estimated values (without 95% CI)	1. Pandemic influenza A/H1N1 1918	Individual	2.2 (1.8 -2.7)	-	1.32 (1.2 – 2.8)	2.2 (1.2 - 3.1)	(Massad et al., 2007, Caley et al., 2008)[1]; (Sertsou et al., 2006, Andreasen et al., 2008, Caley et al., 2008, Chowell et al., 2008a, Rios-Doria and Chowell, 2009) [3,4]	
	2. Pandemic influenza A/ H3N2 1968	Individual			1.2	3.0	(Cooper et al., 2006) [3,4]	
	3. Pandemic influenza A/H1N1 2009	Individual	1.5	1.3 (1.2 - 1.4)	1.34 (1.1 - 2.3)	1.9 (1.3 - 2.9)	(Fraser et al., 2009) [1, 2] (Fraser et al., 2009, White et al., 2009, Yang et al., 2009)[3,4]	
	4. Mutant influenza A/H5N1	Individual	-	-	1.5	1.8	(Ferguson et al., 2005) [3,4]	
	5. Pandemic influenza viruses	Individual	2.1	-	-	-	(Carrat et al., 2006a)[1]	
	6. Seasonal influenza A/H1N1	Individual	1.1	1.2	-	1.4	(Lessler et al., 2007) [1,2,4]	
	7. Seasonal influenza A/H3N2	Individual	1.6 (1.4 - 1.7)	-	1.4 (1.3 - 1.5)	1.7 (1.6 - 1.8)	(Cauchemez et al., 2008) [1, 3,4]	
	8. Influenza viruses	Individual (within-household)	2.3	-	-	-	(Fraser, 2007)[1]	
	9. Influenza viruses	Household level	2.0 (1.2 - 5.9)	-	-	-	(Fraser, 2007, Shaban et al., 2009)[1]	
b) Referenced values	1. Pandemic influenza A/H2N2 1957	-	1.7 (1.7 - 1.7)	-	-	-	(Longini et al., 2004, Arinaminpathy and McLean, 2009)[1]	(Gani et al., 2005) and Longini et al., 2004 based on empirical data
	2. Pandemic influenza A/H2N2 1957/ and A/H3N2 1968	Individual	2.1	2.4	1.9	3.0	(Halloran et al., 2008) [1,2, 3,4]	(Ferguson et al., 2006, Germann et al., 2006) [1,2, 3,4]

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
b) Referenced values	3. Pandemic influenza A/H1N1 2009	Individual	1.5 (1.3 - 1.8)	-	1.3 (1.2 - 1.6)	2.0 (1.3 - 2.2)	(An der Heiden et al., 2009, Gojovic et al., 2009, Medlock and Meyers, 2009, Sypsa and Hatzakis, 2009, Sypsa et al., 2009, Tuite et al., 2009, Yang et al., 2009, Tuite et al., 2010a)[1]; (Kitching et al., 2006, An der Heiden et al., 2009, Boni et al., 2009, Flahault et al., 2009, Medlock and Meyers, 2009, Yang et al., 2009, Perlroth et al., 2010, Tuite et al., 2010a) [3,4]	(Fraser et al., 2009, Yang et al., 2009) and calibrated[1]; (Mills et al., 2004, Glass et al., 2006, Boëlle et al., 2009, Fraser et al., 2009, Nishiura et al., 2009, Yang et al., 2009) and calibrated for Tuite et al 2010a)[3,4]
	4. Pandemic influenza A/H2N2 1957/ and pandemic influenza A/H1N1 2009	Individual	-	1.6	1.2	2.0	(Chao et al., 2010)[2],[3,4]	Calibrated from secondary attack rate and illness attack rates of past pandemic and H1N1 2009[2], [3,4]

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
b) Referenced values	5. Mutant influenza A/H5N1	Individual	1.5 (1.1 – 2.0)	-	1.6 (1.5 – 1.6)	2.4 (2.4 – 2.5)	(Iwami et al., 2007, Milne et al., 2009)[1]; (Milne et al., 2009, Ohkusa and Sugawara, 2009) [3,4]	((Ferguson et al., 2005, Caley et al., 2008) and Iwami et al., 2007 was calibrated value)[1]; (Longini et al., 1988, Ferguson et al., 2005, Longini and Halloran, 2005, Ferguson et al., 2006, Germann et al., 2006, Glass et al., 2006, Caley et al., 2008, Davey et al., 2008, Dubé et al., 2008)[3,4]

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
b) Referenced values	6. Pandemic influenza viruses	-	1.9 (1.5 – 2.5)	2.1 (1.9 - 2.1)	1.4 (1.0 - 1.6)	2.4 (1.4 – 3.0)	(Germann et al., 2006, Wu et al., 2006, Colizza et al., 2007, Duerr et al., 2007a, Nuño et al., 2007a, Roberts et al., 2007, Rizzo et al., 2008, Lunelli et al., 2009)[1] (Germann et al., 2006, Colizza et al., 2007, Nuño et al., 2007a)[2] (Germann et al., 2006, Wu et al., 2006, Colizza et al., 2007, Nuño et al., 2007a, Roberts et al., 2007, Ciofi degli Atti et al., 2008, Gumel et al., 2008, Rizzo et al., 2008, Basta et al., 2009, Lunelli et al., 2009, Wein and Atkinson, 2009) [3,4]	(Glezen, 1996, Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005, Gani et al., 2005, Chowell et al., 2006b, Ferguson et al., 2006, Chowell et al., 2007a, Chowell et al., 2007b, Chowell et al., 2008a)[1]; (Glezen, 1996, Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005, Gani et al., 2005, Chowell et al., 2006b, Ferguson et al., 2006, Chowell et al., 2007a, Chowell et al., 2007b, Chowell et al., 2008a) [3,4]

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
b) Referenced values	7. Novel influenza	-	1.8 (1.2 – 3.8)	-	1.4 (0.3 – 1.4)	2.0 (2.0 – 3.3)	(Grais et al., 2003, Gani et al., 2005, Flahault et al., 2006, Hollingsworth et al., 2006, Saenz et al., 2006, Epstein et al., 2007, Hsu and Shih, 2010)[1]; (Gani et al., 2005, Ferguson et al., 2006, Flahault et al., 2006, Epstein et al., 2007, Nuño et al., 2008)[3,4]	(Burnett and White, 1974, Rvachev L and IM., 1985, Glezen and Couch, 1997, Antia et al., 2003, Mills et al., 2004, Ferguson et al., 2005, Longini et al., 2005)[1;] (Rvachev L and IM., 1985, Longini et al., 2004, Mills et al., 2004, Chowell et al., 2007b)[3,4]
	8. Seasonal influenza/pandemic influenza A/H1N1 1918	-	2.0	-	-	-	(Davey et al., 2008)[1]	(Mills et al., 2004, Glass et al., 2006) [1]
	9. Seasonal influenza/pandemic influenza A/H2N2 1957	-	2.7	-	-	-	(Haber et al., 2007)[1]	(Mills et al., 2004) [1]

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
b) Referenced values	10. Influenza viruses	Individual	1.9 (1.2 - 2.5)	2.27 (2.1 – 2.4)	1.37 (1.3 – 1.6)	2.4 (1.4 -2.73)	(Grais et al., 2004, Eichner et al., 2007, Vardavas et al., 2007, Brauer, 2008, Tsai et al., 2010)[1]; (Brauer, 2008, Tsai et al., 2010)[2] (Brauer, 2008, Tuite et al., 2009, Tsai et al., 2010) [3,4]	(Longini et al., 1988, Flahault et al., 1994, Longini et al., 2004, Mills et al., 2004, Ferguson et al., 2005, Ferguson et al., 2006, Chowell et al., 2007b, Colizza et al., 2007)[1]; (Calibrated from attack rate)[2]; Calibrated[3,4]
c) Assumed values	1. Pandemic influenza A/H3N2 1968	Individual	-	2.5	1.5	3.5	(Glass and Barnes, 2007) [2, 3,4]	
	2. Pandemic influenza A/H1N1 2009	Individual	1.7	1.9	1.4	2.4	(Lee et al., 2009b) [1,2, 3,4]	
	3. Pandemic influenza viruses	Individual	1.9	1.4	1.4 (1.1 - 1.5)	2.0 (1.7 - 3.5)	(Balcan et al., 2009)[1]; (Ajelli and Merler, 2008)[2]; (Gardam et al., 2007, Wood et al., 2007, Ajelli and Merler, 2008, Balcan et al., 2009) [3,4]	
	4. Novel influenza virus	Individual	-	-	1.1	2.4	(Longini et al., 2005) [3,4]	
	5. Seasonal influenza/ and pandemic influenza A/H1N1 1918	Individual	-	-	1.2	2.3	(Bansal et al., 2006) [3,4]	
	6. Influenza viruses	Individual	2.0		1.5	3.0	(Hartvigsen et al., 2007)[1]; (Arino et al., 2008)[3,4]	

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
a.1) Estimated values (without 95% CI)	**B. Bird - bird**							
	1(a). Avian influenza A/H5N1	Within-flock (1 day infectious period)	2.3 (2.0 – 2.6)	-	-	-	(Tiensin et al., 2007)[1]	
	1(b). Avian influenza A/H5N1	Within-flock (4 day infectious period)	2.6 (2.0 – 3.5)	-	-	-	(Tiensin et al., 2007) [1]	
	2(a). Avian influenza A/ H5N2 (highly pathogenic)	Between flock level	1.0 (0.0 – 2.4)	-	-	-	(van der Goot et al., 2003) [1]	
	2(b). Avian influenza A/H5N2 (low pathogenic)	Between flock level	0.95 (0.0 – 2.3)	-	-	-	(van der Goot et al., 2003) [1]	
a.2) Estimated values (without 95% CI)	1(a). Avian influenza A/H5N1	Between village level	2.5 (2.2 – 2.7)		2.0	2.1	(Ward et al., 2009)[3]	(Two R_0means were estimated by SI modeling and Epidemic doubling time methods)[1] (Ro estimated using nearest infectious neighbours using road distance (low value) and Euclidean distance (upper value))[3]
	1(b). Avian influenza A/H5N1	Individual (within cage)		-	25.0	66.0	(Savill et al., 2006)[3,4]	Lower and upper ranged are for caged and floor reared birds
	2. Avian influenza A/H7N1	Between farm	-	-	0.6	1.8	(Mannelli et al., 2007)[1]	

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
a.2) Estimated values (without 95% CI)	3(a). Avian influenza A/H7N7	Individual level			1.3	-	(van der Goot et al., 2005) [3]	
	3(b). Avian influenza A/H7N7	Between farm	3.3 (1.3 - 5.2)		3.6 (3.1 – 4.0)	6.7 (6.5 – 6.9)	(Le Menach et al., 2006, Bavinck et al., 2009)[1]; (Stegeman et al., 2004, Le Menach et al., 2006)[3,4]	
b) Referenced values	1. Avian influenza A/H5N1	Individual	-	-	25.0	66.0	(Sharkey et al., 2008) [3,4]	(Savill et al., 2006) [3,4]
	2. Avian influenza A/H7N7	Individual	-	5.0	0.8	6.5	(Iwami et al., 2009)[2, 3,4]	(Stegeman et al., 2004) [2, 3,4]
c) Assumed values	**Zoonotic spread**							
	a. Human - human							
	1. Mutant influenza A/H5N1	Individual	-	-	2.0 (0.6 – 3.5)	4.1 (1.1 – 7.1)	(Iwami et al., 2007, Kim et al., 2010) [3,4]	
	b. Swine - swine							
	1. Novel influenza virus	Individual	2.0	-	-	-	(Saenz et al., 2006)[1]	
	c. Bird-bird							
	1. Mutant influenza A/H5N1	Individual	1.1	-	0.4 (0.1 – 0.8)	1.8 (1.1 - 2.5)	(Iwami et al., 2007, Kim et al., 2010) [1, 3,4]	Derived from transmission rates [1, 3,4]
2. Generation intervals (day)	**A. Human- human**			-				
a) Estimated values	1. Pandemic influenza A/ H1N1 1918	Individual	2.6	-			(Caley et al., 2008)[1]	
	2. Pandemic influenza A/H1N1 2009	Individual	3.5	-	2.6 (2.2 – 4.0)	2.9 (2.3 – 5.0)	(Yang et al., 2009)[1]; (White et al., 2009, Yang et al., 2009, Tuite et al., 2010b)[3,4]	
	3. Pandemic influenza viruses	Individual	2.4	-	1.0	3.9	(Carrat et al., 2006a)[1,3,4]	
	4. Seasonal influenza A/H1N1	Individual	2.1 (1.9 – 2.3)	-	1.6 (1.5 – 1.6)	3.3 (2.7 – 3.8)	(Canadian Food Inspection Agency, Lessler et al., 2007)[1, 3,4]	

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
a) Estimated values	5. Seasonal influenza A/H3N2	Individual	3.1	-	2.2	4.0	(Canadian Food Inspection Agency)[1,2, 3]	
	6. Influenza viruses	Individual	3.5 (3.4 – 3.6)	-	2.9	4.3	(Canadian Food Inspection Agency, Cowling et al., 2009)[1]; (Cowling et al., 2009)[3,4]	
b) Referenced values	1. Pandemic influenza A/H1N1 1918	Individual	-	-	2.6	4.0	(Andreasen et al., 2008)[2,3]	(Mills et al., 2004, Longini et al., 2005, Feighner et al., 2009)[2,3]
	2. Pandemic influenza A/H2N2 1957/ and pandemic influenza A/H1N1 2009	Individual	3.4	-	-	-	(Chao et al., 2010)[1]	(Cowling et al., 2009, Yang et al., 2009)[1];
	3. Pandemic influenza A/H1N1 2009	Individual	3.1 (1.9 – 4.6)	-	1.6 (1.0 – 6.6)	5.0 (2.7 – 3.8)	(Boëlle et al., 2009, Flahault et al., 2009, Fraser et al., 2009)[1,2,3]	(Canadian Food Inspection Agency, Ferguson et al., 2005, Dubé et al., 2008, Ansart et al., 2009, Boëlle et al., 2009, Fraser et al., 2009)[1,2,3]
	4. Mutant H5N1	Individual	2.7 (2.6 – 2.9)	-	2.5 (2.1 – 3.0)	2.9 (2.7 – 3.0)	(Ferguson et al., 2005, Milne et al., 2009)[1,2,3]	((Fox et al., 1982) and adjusted from Ro by Milne et al., 2009)[1,2,3]
	5. Pandemic influenza virus	Individual	2.9 (2.6 – 3.2)	-	2.6	3.8	(Wu et al., 2006, Ciofi degli Atti et al., 2008)[1]; (Wu et al., 2006)[3,4]	(Ferguson et al., 2006)[1,3,4]
	6. Seasonal influenza A/H3N2	Individual	2.4	-	-	-	(Cauchemez et al., 2008)[1];	(Cauchemez et al., 2004)[1]

Table S10: (continued)

Disease transmission parameters	Spread type and agent	Subject of interest	Median of means (Range)	Median of medians (Range)	Median of min. values (Range)	Median of max. values (Range)	Article	Source Reference sources
b) Referenced values	7. Influenza viruses	Individual	2.8	-			(Fraser, 2007, van den Dool et al., 2008)[1]	(Hirotsu et al., 2004, Wallinga and Lipsitch, 2007) [1]
c) Assumed values	1. Pandemic influenza A/H1N1 1918		6.0	-	3	6.0	(Chowell et al., 2007b)[1]; (Chowell et al., 2008a)[3,4]	Derived from mean latent +mean infectious period
	2. Pandemic influenza A/H3N2 1968	Individual	3.9 (3.5 – 4.2)	-			(Cooper et al., 2006, Glass and Barnes, 2007) [1]	
	3. Pandemic influenza viruses	Individual		-	2.8	4.0	(Wood et al., 2007) [3,4]	
	4. Novel influenza virus	Individual	2.6	-			(Ferguson et al., 2006, Hollingsworth et al., 2006)[1]	

Note: (a) Estimated values are those estimated from empirical data of experimental or observational studies; (b) Referenced values refer to those values taken from other articles or sources; (c) Assumed values are values assumed based on expert opinion or unpublished data sources. Summary estimates are medians and ranges of means, medians, minimum and maximum values of two or more articles. Single value represented value from either one article or same value from two or more articles. Superscript numbers on articles and reference sources correspond to columns of mean =1; median =2; minimum =3; and maximum = 4.

Table S11: Summary of intervention parameters either estimated from experimental and observational studies, referenced or assumed for modeling influenza infection in human and bird populations along with list of articles and references.

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	References
I. Human						
A. Antiviral treatment AV						
a) Estimated values	1. AV efficacy (%)	-	70.0	75.5 (61.0–90.0)	(Lipsitch et al., 2003)[2]; (Hayden and Aoki, 1999b, Lipsitch et al., 2003)[3]	
b) Referenced values	1. AV efficacy (%)	-	30.0 (28.0–30.0)	70.0 (30.0–100)	(Longini et al., 2004, Carrat et al., 2006a, Ferguson et al., 2006, Nuño et al., 2007a, Ciofi degli Atti et al., 2008, Davey and Glass, 2008, Gumel et al., 2008, Rizzo et al., 2008, Sypsa et al., 2009, Perlroth et al., 2010)[2]; (Longini et al., 2004, Gani et al., 2005, Carrat et al., 2006a, Ferguson et al., 2006, Flahault et al., 2006, Germann et al., 2006, Gardam et al., 2007, Nuño et al., 2007a, Roberts et al., 2007, Ciofi degli Atti et al., 2008, Davey and Glass, 2008, Gumel et al., 2008, Rizzo et al., 2008, Sypsa et al., 2009, Chao et al., 2010, Perlroth et al., 2010, Tsai et al., 2010)[3]	(Meat and Livestock Australia, Galbraith et al., 1969, Hayden et al., 2000, Welliver et al., 2001, Halloran et al., 2002, Lipsitch et al., 2003, Hayden et al., 2004, Longini et al., 2004, Ferguson et al., 2005, Longini et al., 2005, Ferguson et al., 2006)[2]; (Meat and Livestock Australia, Hayden and Aoki, 1999b, Hayden et al., 2000, Welliver et al., 2001, Lipsitch et al., 2003, Stiver, 2003, Hayden et al., 2004, Trapman et al., 2004, Ferguson et al., 2005, Gani et al., 2005, Longini and Halloran, 2005, Ferguson et al., 2006, Jefferson et al., 2006, Yang et al., 2007, Halloran et al., 2008)[3]

Table S11: (continued)

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	References
b) Referenced values	2. Reduction in infectiousness (%)	-	30.0	62.0 (28.0–80.0)	(Nuño et al., 2007a, Gumel et al., 2008)[2]; (Ferguson et al., 2005, Longini et al., 2005, Carrat et al., 2006a, Ferguson et al., 2006, Flahault et al., 2006, Germann et al., 2006, Colizza et al., 2007, Duerr et al., 2007b, Gardam et al., 2007, Nuño et al., 2007a, Roberts et al., 2007, Ciofi degli Atti et al., 2008, Davey and Glass, 2008, Gumel et al., 2008, Sypsa et al., 2009, Chao et al., 2010, Perlroth et al., 2010, Tsai et al., 2010)[3]	(Harper et al., 2004, Longini et al., 2004)[2];(Meat and Livestock Australia, Hayden and Aoki, 1999b, Hayden et al., 2000, Welliver et al., 2001, Halloran et al., 2002, Harper et al., 2004, Longini et al., 2004, Ferguson et al., 2005, Gani et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Jefferson et al., 2006, Yang Y et al., 2006, Yang et al., 2007)[2,3]
	3. Reduction in susceptibility (%)	-	30.0 (25.0–30.0)	35.0 (30.0–90.0)	(Doyle et al., 2006, Flahault et al., 2006, Germann et al., 2006, Gardam et al., 2007, Nuño et al., 2007a, Xu et al., 2007, Gumel et al., 2008, Rizzo et al., 2008, Tsai et al., 2010)[2]; (Ferguson et al., 2005, Longini et al., 2005, Carrat et al., 2006a, Doyle et al., 2006, Flahault et al., 2006, Gardam et al., 2007, Nuño et al., 2007a, Xu et al., 2007, Ciofi degli Atti et al., 2008, Davey and Glass, 2008, Gumel et al., 2008, Rizzo et al., 2008, Sypsa et al., 2009, Chao et al., 2010, Perlroth et al., 2010)[3]	(Meat and Livestock Australia, Gross et al., 1995, Stilianakis et al., 1998, Hayden and Aoki, 1999b, Hayden et al., 2000, Welliver et al., 2001, Fock et al., 2002, Kawai et al., 2003, Lipsitch et al., 2003, Hayden et al., 2004, Longini et al., 2004, Gani et al., 2005, Longini et al., 2005, Jefferson et al., 2006, Yang et al., 2007)[2]; (Meat and Livestock Australia, Gross et al., 1995, Stilianakis et al., 1998, Hayden and Aoki, 1999b, Hayden et al., 2000, Fock et al., 2002, Kawai et al., 2003, Lipsitch et al., 2003, Hayden et al., 2004, Longini et al., 2004, Ferguson et al., 2005, Gani et al., 2005, Longini et al., 2005, Ferguson et al., 2006, Jefferson et al., 2006, Yang et al., 2007)[3];

Table S11: (continued)

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	References
b) Referenced values	4. AV coverage (%)	-	50.0 (0.0–60.0)	90.0 (50.0 – 100)	(Nuño et al., 2007a, Davey and Glass, 2008, Gumel et al., 2008, An der Heiden et al., 2009, Perlroth et al., 2010)[2]; (Ferguson et al., 2005, Wu et al., 2006, Nuño et al., 2007a, Xu et al., 2007, Davey and Glass, 2008, Gumel et al., 2008, An der Heiden et al., 2009, Gojovic et al., 2009, Perlroth et al., 2010)[3]	(Stilianakis et al., 1998, Meltzer et al., 1999, Ferguson et al., 2005, Gani et al., 2005, Ferguson et al., 2006)[2, 3]
	5. AV treatment duration (day)	-	10.0 (5.0–10.0)	10.0 (5.0–10.0)	(Carrat et al., 2006a, Germann et al., 2006, Ciofi degli Atti et al., 2008, Davey and Glass, 2008, Halloran et al., 2008, Sypsa et al., 2009, Perlroth et al., 2010, Tsai et al., 2010)[2,3]	(Meat and Livestock Australia, Hayden and Aoki, 1999b, Hayden et al., 2000, Welliver et al., 2001, Halloran et al., 2002, Longini et al., 2004, Ferguson et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Yang et al., 2007)[2,3]
	6. AV use compliance (%)	-	48.0 (5.0 – 90)	90.0	(Sypsa et al., 2009, Chao et al., 2010)[2]; (Sypsa et al., 2009)[3]	(Longini et al., 2004, Germann et al., 2006, Halloran et al., 2008)[2]; (Germann et al., 2006, Halloran et al., 2008)[3]
c) Assumed values	1. AV efficacy (%)	-	50.0	30 (30.0–100)	(Gojovic et al., 2009)[2]; (Doyle et al., 2006, Wu et al., 2006, Duerr et al., 2007b, Das et al., 2008, Arinaminpathy and McLean, 2009, Gojovic et al., 2009, Yasuda and Suzuki, 2009)[3]	
	2. Reduction in infectiousness (%)	-	-	62.0 (30.0–100.0)	(Gani et al., 2005, Wu et al., 2006, Duerr et al., 2007b, Das et al., 2008, Yasuda and Suzuki, 2009)[3]	
	3. Reduction in susceptibility (%)	-	-	30 (30.0–100)	(Ferguson et al., 2006, Wu et al., 2006, Duerr et al., 2007b, Das et al., 2008, Yasuda and Suzuki, 2009)[3]	

Table S11: (continued)

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	References
c) Assumed values	4. AV coverage (%)	-	50.0 (2.0–80.0)	100.0 (6.0–100)	(Gani et al., 2005, Longini et al., 2005, Carrat et al., 2006a, Ferguson et al., 2006, Germann et al., 2006, Colizza et al., 2007, Duerr et al., 2007a, Gardam et al., 2007, Ciofi degli Atti et al., 2008, Rizzo et al., 2008, Arinaminpathy and McLean, 2009, Yasuda and Suzuki, 2009, Tsai et al., 2010)[2]; (Gani et al., 2005, Longini et al., 2005, Carrat et al., 2006a, Doyle et al., 2006, Ferguson et al., 2006, Germann et al., 2006, Colizza et al., 2007, Duerr et al., 2007a, Eichner et al., 2007, Gardam et al., 2007, Roberts et al., 2007, Arinaminpathy and McLean, 2008b, Ciofi degli Atti et al., 2008, Halloran et al., 2008, Rizzo et al., 2008, Sypsa et al., 2009, Yasuda and Suzuki, 2009, Chao et al., 2010, Tsai et al., 2010)[3]	Coverage of 2% (lowest minimum value) and 6% (lowest max. value) are global coverage % (Colizza et al., 2007)[2,3]
	5. AV treatment duration (day)	-	7.5 (5 - 10)	5.0	(Longini et al., 2004, Ferguson et al., 2005, Gani et al., 2005, Doyle et al., 2006, Ferguson et al., 2006, Wu et al., 2006, Duerr et al., 2007b, Gojovic et al., 2009, Chao et al., 2010)[2,3]	
	6. AV use compliance (%)	-	5.0	100 (80.0–100)	(Longini et al., 2004, Doyle et al., 2006, Ferguson et al., 2006, Wu et al., 2006, Duerr et al., 2007b, Davey and Glass, 2008, Halloran et al., 2008, Gojovic et al., 2009, Perlroth et al., 2010)[2,3]	

Table S11: (continued)

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	References
B. Vaccination	1.					
a) Estimated values	2. Vaccine efficacy (%)	-	38.75 (19.0–58.5)	57.5 (47.0–68.0)	(Vu et al., 2002, Hayden et al., 2004)[2,3]	
b) Referenced values	1. Vaccine efficacy (%)	-	40.0 (20.0–70.0)	73.0 (30.0–100)	(Longini et al., 2004, Bansal et al., 2006, Doyle et al., 2006, Nuño et al., 2007a, Ciofi degli Atti et al., 2008, Gumel et al., 2008, van den Dool et al., 2008, Gojovic et al., 2009, Milne et al., 2009, Sypsa and Hatzakis, 2009, Tuite et al., 2009, Yang et al., 2009, Tuite et al., 2010a)[2]; (Longini et al., 2004, Longini et al., 2005, Bansal et al., 2006, Doyle et al., 2006, Kitching et al., 2006, Nuño et al., 2007a, Ciofi degli Atti et al., 2008, Gumel et al., 2008, van den Dool et al., 2008, Gojovic et al., 2009, Milne et al., 2009, Sypsa et al., 2009, Tuite et al., 2009, Yang et al., 2009, Chao et al., 2010, Tuite et al., 2010a)[3]	(Gross et al., 1995, Belshe et al., 1998, Halloran et al., 1999, Hayden and Aoki, 1999b, Belshe et al., 2000, Longini et al., 2000, Welliver et al., 2001, Fock et al., 2002, Halloran et al., 2002, Vu et al., 2002, Kawai et al., 2003, Lipsitch et al., 2003, Demicheli et al., 2004, Harper et al., 2004 {Fiore, 2008 #1582 , Hayden et al., 2004, Longini et al., 2004, Zangwill and Belshe, 2004, Jefferson et al., 2005, Bansal et al., 2006, Goodwin et al., 2006, Rivetti et al., 2006, Smith, 2006, Yang et al., 2007, Basta et al., 2008, Fiore et al., 2008)[2, 3];

Table S11: (continued)

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	References
b) Referenced values	2. Reduction in infectiousness (%)	-	30.0 (20.0–50.0)	70.0 (40.0–90.0)	(Bansal et al., 2006, Nuño et al., 2007a, Gumel et al., 2008, Basta et al., 2009, Gojovic et al., 2009, Sypsa and Hatzakis, 2009, Tuite et al., 2010a)[2]; (Longini et al., 2005, Bansal et al., 2006, Nuño et al., 2007a, Gumel et al., 2008, Basta et al., 2009, Gojovic et al., 2009, Sypsa et al., 2009, Chao et al., 2010, Tuite et al., 2010a)[3]	(Halloran et al., 1999, Vu et al., 2002, Harper et al., 2004, Longini et al., 2004, Jefferson et al., 2005, Bansal et al., 2006, Goodwin et al., 2006, Basta et al., 2008, Centers for Disease Control and Prevention (CDC), 2009)[2]; (Halloran et al., 1999, Hayden and Aoki, 1999b, Hayden et al., 2000, Welliver et al., 2001, Vu et al., 2002, Harper et al., 2004, Longini et al., 2004, Jefferson et al., 2005, Bansal et al., 2006, Goodwin et al., 2006, Yang et al., 2007, Basta et al., 2008, Centers for Disease Control and Prevention (CDC), 2009)[3]
	3. Vaccine immune delay (days)	-	7.0	42.0	(Milne et al., 2009)[2,3]	(Bresson et al., 2006, Leroux-Roels et al., 2007) [2,3]
	4. Vaccination coverage (%)	60.0 (50.0–60.0)	25.5 (18.0–26.0)	87.5 (69.0–100.0)	(Vardavas et al., 2007, Ciofi degli Atti et al., 2008, Rizzo et al., 2008, van den Dool et al., 2008)[1]; (van den Dool et al., 2008, Tuite et al., 2009, Tuite et al., 2010a)[2]; (Germann et al., 2006, van den Dool et al., 2008, Tuite et al., 2009, Tsai et al., 2010, Tuite et al., 2010a)[3]	(Hayward et al., 2006) and the govt. report[1]; (Hayward et al., 2006, Kwong et al., 2008, Moran et al., 2009)[2]; (Kwong et al., 2008, Moran et al., 2009)[3];

Table S11: (continued)

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	References
c) Assumed values	1. Vaccine efficacy (%)	-	30.0 (5.0–50.0)	70.0 (30.0–100)	(Weycker et al., 2005, Ferguson et al., 2006, Germann et al., 2006, Rizzo et al., 2008, Basta et al., 2009, Lunelli et al., 2009, Medlock and Meyers, 2009, Yasuda and Suzuki, 2009, Tsai et al., 2010)[2]; (Halloran et al., 2002, Weycker et al., 2005, Carrat et al., 2006a, Ferguson et al., 2006, Flahault et al., 2006, Germann et al., 2006, Glass and Barnes, 2007, Hartvigsen et al., 2007, Vardavas et al., 2007, Das et al., 2008, Davey and Glass, 2008, Rizzo et al., 2008, Basta et al., 2009, Lunelli et al., 2009, Medlock and Meyers, 2009, Shaban et al., 2009, Yasuda and Suzuki, 2009, Perlroth et al., 2010, Tsai et al., 2010)[3]	
	2. Reduction in infectiousness (%)	-	50.0 (30.0–50.0)	80.0 (40.0–100)	(Halloran et al., 2002, Ferguson et al., 2006, Germann et al., 2006, Glass and Barnes, 2007, Hartvigsen et al., 2007, Vardavas et al., 2007, Das et al., 2008, Shaban et al., 2009, Tsai et al., 2010)[2,3];	
	3. Vaccine immune delay (days)		15.0 (0.0–15.0)	14.0 (0.0–14.0)	(Carrat et al., 2006a, Nuño et al., 2007a, Ciofi degli Atti et al., 2008, Rizzo et al., 2008)[2]; (Ferguson et al., 2006, Kitching et al., 2006, Vardavas et al., 2007, van den Dool et al., 2008, Tuite et al., 2009, Chao et al., 2010)[3]	

Table S11: (continued)

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	References
c) Assumed values	4. Vaccination coverage (%)	50.0 (30.0–50.0)	20.0 (0.0–50.0)	75.0 (7.0–100)	(Longini et al., 2004, Flahault et al., 2006, Kitching et al., 2006, Basta et al., 2009, Flahault et al., 2009, Gojovic et al., 2009, Yang et al., 2009)[1]; (Halloran et al., 2002, Longini et al., 2004, Longini et al., 2005, Weycker et al., 2005, Bansal et al., 2006, Ferguson et al., 2006, Kitching et al., 2006, Epstein et al., 2007, Hartvigsen et al., 2007, Basta et al., 2009, Flahault et al., 2009, Gojovic et al., 2009, Milne et al., 2009, Yang et al., 2009)[2]; (Halloran et al., 2002, Longini et al., 2004, Longini et al., 2005, Weycker et al., 2005, Bansal et al., 2006, Carrat et al., 2006a, Doyle et al., 2006, Ferguson et al., 2006, Kitching et al., 2006, Epstein et al., 2007, Glass and Barnes, 2007, Hartvigsen et al., 2007, Davey and Glass, 2008, Basta et al., 2009, Flahault et al., 2009, Gojovic et al., 2009, Milne et al., 2009, Shaban et al., 2009, Sypsa and Hatzakis, 2009, Yang et al., 2009, Yasuda and Suzuki, 2009, Chao et al., 2010, Perlroth et al., 2010)[3]	

Table S11: (continued)

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	References
C. School closure						
c) Assumed values	1. School closure contact reduction (%)	75.0 (50.0 – 80.0)	31.5 (30.0 – 33.0)	100 (70.0–100)	(Ohkusa and Sugawara, 2007, Rizzo et al., 2008, Lunelli et al., 2009)[1;] (Lunelli et al., 2009, Yasuda and Suzuki, 2009)[2]; (Haber et al., 2007, Ciofi degli Atti et al., 2008, Davey and Glass, 2008, Lunelli et al., 2009, Sypsa and Hatzakis, 2009, Yasuda and Suzuki, 2009, Perlroth et al., 2010)[3]	
c) Assumed values	2. School closure duration (days)	14.0 (7.0 – 28.0)	7.0 (7.0–60.0)	25.0 (7.0–300.0)	(Haber et al., 2007, Gojovic et al., 2009, Lunelli et al., 2009)[1]; (Haber et al., 2007, Gojovic et al., 2009, Lee et al., 2009b, Lunelli et al., 2009, Chao et al., 2010)[2]; (Haber et al., 2007, Roberts et al., 2007, Rizzo et al., 2008, Gojovic et al., 2009, Lee et al., 2009b, Lunelli et al., 2009, Yasuda and Suzuki, 2009)[3]	
	3. School closure delay (days)	-	0.0–14.0	7.0 (0.0– 56.0)	(Germann et al., 2006, Ohkusa and Sugawara, 2007, Cauchemez et al., 2008, Rizzo et al., 2008, Gojovic et al., 2009, Yasuda and Suzuki, 2009, Tsai et al., 2010)[2]; (Ferguson et al., 2006, Haber et al., 2007, Ohkusa and Sugawara, 2007, Ciofi degli Atti et al., 2008, Rizzo et al., 2008, Lee et al., 2009b, Yasuda and Suzuki, 2009)[3]	

Table S11: (continued)

Intervention type	Parameter	Median of means (Range)	Median of min. values (Range)	Median of max. values (Range)	Articles	References
C. Quarantine						
c) Assumed values	1. Quarantine contact reduction (%)	50.0	55.0 (40.0–60.0)	85.0 (30.0–100)	(Nuño et al., 2007a)[1]; (Ohkusa and Sugawara, 2007, Davey and Glass, 2008, An der Heiden et al., 2009, Perlroth et al., 2010)[2]; (Sattenspiel and Herring, 2003, Longini et al., 2005, Wu et al., 2006, Duerr et al., 2007b, Ohkusa and Sugawara, 2007, Roberts et al., 2007, Davey and Glass, 2008, An der Heiden et al., 2009, Shaban et al., 2009, Perlroth et al., 2010)[3]	
	2. Quarantine duration (days)	10.0 (2.0–10.0)	1.0	7.0 (3.0–21.0)	(Haber et al., 2007, Davey and Glass, 2008, Perlroth et al., 2010)[1]; (Haber et al., 2007)[2]; (Ferguson et al., 2005, Carrat et al., 2006a, Ferguson et al., 2006, Wu et al., 2006, Haber et al., 2007, Roberts et al., 2007, Das et al., 2008, Halloran et al., 2008, Chao et al., 2010)[3]	
II. Birds						
C. Quarantine						
c) Assumed values	1. Quarantine period (days)	21.0–31.0	-	-	(Sharkey et al., 2008)[1]	

Note: (a) Estimated values are those estimated from empirical data of experimental or observational studies; (b) Referenced values refer to those values taken from other articles or sources; (c) Assumed values are values assumed based on expert opinion or unpublished data sources. Summary estimates are medians and ranges of means, medians, minimum and maximum values of two or more articles. Single value represented value from either one article or same value from two or more articles. Superscript numbers on articles and reference sources correspond to columns of mean =1; minimum =2; and maximum = 3.

Reference

Addy, C. L., I. M. Longini, Jr. and M. Haber, 1991: A generalized stochastic model for the analysis of infectious disease final size data. Biometrics, 47, 961-974.

Advisory Committee on Immunization Practices (ACIP), Presentation slides: special July 2009 meeting. Atlanta GA: CDC, 2009. www.cdc.gov/vaccines/recs/acip/slides-july09-flu.htm.

Ajelli, M. and S. Merler, 2008: The impact of the unstructured contacts component in influenza pandemic modeling. PLoS One, 3, e1519.

Ander Heiden, M., U. Buchholz, G. Krause, G. Kirchner, H. Claus and W. H. Haas, 2009: Breaking the waves: modelling the potential impact of Public Health measures to defer the epidemic peak of novel influenza A/H1N1. PLoS One, 4, e8356.

Anderson, R. and R. May, 1991: Infectious diseases of humans: dynamics and controls. Oxford: Oxford University Press.

Andreasen, V., C. Viboud and L. Simonsen, 2008: Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implications for pandemic control strategies. J. Infect. Dis., 197, 270-278.

Anonymous, 2007: Outbreak of highly pathogenic H5N1 avian influenza in Suffolk in January 2007. Available at: http://www.defra.gov.uk/animalh/diseases/notifiable/disease/ai/pdf/epid_findings050407.pdf (accessed on 28 October 2011

Ansart, S., C. Pelat, P. Y. Boelle, F. Carrat, A. Flahault and A. J. Valleron, 2009: Mortality burden of the 1918-1919 influenza pandemic in Europe. Influenza Other Respi. Viruses, 3, 99-106.

Antia, R., R. R. Regoes, J. C. Koella and C. T. Bergstrom, 2003: The role of evolution in the emergence of infectious diseases. Nature, 426, 658-661.

Aparicio, J. P. and M. Pascual, 2007: Building epidemiological models from R0: an implicit treatment of transmission in networks. Proc. R. Soc. Lond. B. Biol. Sci., 274, 505-512.

Arinaminpathy, N. and A. R. McLean, 2008a: Antiviral treatment for the control of pandemic influenza: some logistical constraints. J. R. Soc. Interface, 5, 545-553.

Arinaminpathy, N. and A. R. McLean, 2008b: Antiviral treatment for the control of pandemic influenza: some logistical constraints. J. R. Soc. Interface., 5, 545-553.

Arinaminpathy, N. and A. R. McLean, 2009: Logistics of control for an influenza pandemic. Epidemics, 1, 83-88.

Arino, J., F. Brauer, P. van den Driessche, J. Watmough and J. Wu, 2008: A model for influenza with vaccination and antiviral treatment. J. Theor. Biol., 253, 118-130.

Arino, J., R. Jordan and P. van den Driessche, 2007: Quarantine in a multi-species epidemic model with spatial dynamics. Math. Biosci., 206, 46-60.

Aznar, M. N., M. A. Stevenson, L. Zarich and E. A. Leon, 2011: Analysis of cattle movements in Argentina, 2005. Prev. Vet. Med., 98, 119-127.

Balcan, D., V. Colizza, B. GonÃ§alves, H. Hu, J. J. Ramasco and A. Vespignani, 2009: Multiscale mobility networks and the spatial spreading of infectious diseases. Proc. Natl. Acad. Sci. U. S. A., 106, 21484-21489.

Bansal, S., B. Pourbohloul and L. A. Meyers, 2006: A Comparative Analysis of Influenza Vaccination Programs. PLoS Med., 3, e387.

Barry, J. M., C. Viboud and L. Simonsen, 2008: Cross-protection between successive waves of the 1918-1919 influenza pandemic: epidemiological evidence from US Army camps and from Britain. J. Infect. Dis., 198, 1427-1434.

Basta, N. E., D. L. Chao, M. E. Halloran, L. Matrajt and I. M. Longini, Jr., 2009: Strategies for pandemic and seasonal influenza vaccination of schoolchildren in the United States. Am. J. Epidemiol., 170, 679-686.

Basta, N. E., M. E. Halloran, L. Matrajt and I. M. Longini, Jr., 2008: Estimating influenza vaccine efficacy from challenge and community-based study data. Am. J. Epidemiol., 168, 1343-1352.

Bavinck, V., A. Bouma, M. van Boven, M. E. H. Bos, E. Stassen and J. A. Stegeman, 2009: The role of backyard poultry flocks in the epidemic of highly pathogenic avian influenza virus (H7N7) in the Netherlands in 2003. Prev. Vet. Med., 88, 247-254.

Bell, D. M., 2006: Non-pharmaceutical interventions for pandemic influenza, national and community measures. Emerg. Infect. Dis., 12, 88-94.

Belshe, R. B., W. C. Gruber, P. M. Mendelman, I. Cho, K. Reisinger, S. L. Block, J. Wittes, D. Iacuzio, P. Piedra, J. Treanor, J. King, K. Kotloff, D. I. Bernstein, F. G. Hayden, K. Zangwill, L. Yan and M. Wolff, 2000: Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. J. Pediatr., 136, 168-175.

Belshe, R. B., P. M. Mendelman, J. Treanor, J. King, W. C. Gruber, P. Piedra, D. I. Bernstein, F. G. Hayden, K. Kotloff, K. Zangwill, D. Iacuzio and M. Wolff, 1998: The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N. Engl. J. Med., 338, 1405-1412.

Blaskovic, D., V. Rathova, R. Skoda, D. Kociskova and M. M. Kaplan, 1970: Experimental infection of weanling pigs with A-swine influenza virus. 1. Epidemiology and serological Response. Bull. World Health Organ., 42, 757-765.

Boëlle, P. Y., P. Bernillon and J. C. Desenclos, 2009: A preliminary estimation of the reproduction ratio for new influenza A(H1N1) from the outbreak in Mexico, March-April 2009. Euro Surveill., 14, pii=19205.

Boni, M. F., B. H. Manh, P. Q. Thai, J. Farrar, T. T. Hien, N. T. Hien, N. Van Kinh and P. Horby, 2009: Modelling the progression of pandemic influenza A (H1N1) in Vietnam and the opportunities for reassortment with other influenza viruses. BMC Med., 7, 43.

Bos, M. E. H., M. v. Boven, M. Nielen, A. Bouma, A. R. W. Elbers, G. Nodelijk, G. Koch, A. Stegeman and M. C. M. d. Jong, 2007: Estimating the day of highly pathogenic avian influenza (H7N7) virus introduction into a poultry flock based on mortality data. Vet. Res., 38, 493-504.

Brauer, F., 2008: Epidemic models with heterogeneous mixing and treatment. Bull. Math. Biol., 70, 1869-1885.

Bresson, J. L., C. Perronne, O. Launay, C. Gerdil, M. Saville, J. Wood, K. Hoschler and M. C. Zambon, 2006: Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: phase I randomised trial. Lancet, 367, 1657-1664.

Brookes, S. M., A. Nunez, B. Choudhury, M. Matrosovich, S. C. Essen, D. Clifford, M. J. Slomka, G. Kuntz-Simon, F. Garcon, B. Nash, A. Hanna, P. M. Heegaard, S. Queguiner, C. Chiapponi, M. Bublot, J. M. Garcia, R. Gardner, E. Foni, W. Loeffen, L. Larsen, K. Van Reeth, J. Banks, R. M. Irvine and I. H. Brown, 2010: Replication, pathogenesis and transmission of pandemic (H1N1) 2009 virus in non-immune pigs. PLoS One, 5, e9068. doi:9010.1371/journal.pone.0009068.

Brown, I. H., 2000: The epidemiology and evolution of influenza viruses in pigs. Vet. Microbiol., 74, 29-46.

Burnett, M. and D. White, 1974: Natural History of Infectious Disease. 4th ed. Cambridge University Press, Cambridge.

Caley, P., D. J. Philp and K. McCracken, 2008: Quantifying social distancing arising from pandemic influenza. J. R. Soc. Interface, 5, 631-639.

Canadian Food Inspection Agency, Canadian Cattle Identification Program. URL: http://www.inspection.gc.ca/animals/terrestrial-animals/traceability/cattle-identification/eng/1328829147320/1328851840083 (Last accessed on 29 April 2013).

Capua, I. and D. J. Alexander, 2004: Human health implications of avian influenza viruses and paramyxoviruses. Eur. J. Clin. Microbiol. Infect. Dis., 23, 1-6.

Carpenter, C. and L. Sattenspiel, 2009: The design and use of an agent-based model to simulate the 1918 influenza epidemic at Norway House, Manitoba. Am. J. Hum. Biol, 21, 290-300.

Carrat, F., J. Luong, H. Lao, A. V. Salle, C. Lajaunie and H. Wackernagel, 2006: A 'small-world-like' model for comparing interventions aimed at preventing and controlling influenza pandemics. BMC Med., 4, 1-14

Carrat, F., J. Luong, H. Lao, A. V. Salle, C. Lajaunie and H. Wackernagel, 2006b: A 'small-world-like' model for comparing interventions aimed at preventing and controlling influenza pandemics. BMC Med., 4, 1-14.

Castillo-Chavez, C., H. W. Hethcote, V. Andreasen, S. A. Levin and W. M. Liu, 1989: Epidemiological models with age structure, proportionate mixing, and cross-immunity. J. Math. Biol., 27, 233-258.

Cauchemez, S., F. Carrat, C. Viboud, A. J. Valleron and P. Y. Boelle, 2004: A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. Stat. Med., 23, 3469-3487.

Cauchemez, S., A.-J. Valleron, P.-Y. BoÃ«lle, A. Flahault and N. M. Ferguson, 2008: Estimating the impact of school closure on influenza transmission from Sentinel data. Nature, 452, 750.

Centers for Disease Control and Prevention (CDC), 2006: Prevention and control of influenza: clinical description and diagnosis. Available at http://www.cdc.gov/flu/professionals/diagnosis/clinicali (accessed on 19 April 2011).

Centers for Disease Control and Prevention (CDC), 2009: Swine influenza A (H1N1) infection in two children--Southern California, March-April 2009. MMWR. Morb. Mortal. Wkly. Rep., 58, 400-402.

Chao, D. L., M. E. Halloran, V. J. Obenchain and I. M. Longini, 2010: FluTE, a Publicly Available Stochastic Influenza Epidemic Simulation Model. PLoS Comput. Biol., 6, e1000656.

Chen, S.-C. and C.-M. Liao, 2010: Probabilistic indoor transmission modeling for influenza (sub)type viruses. J. Infect., 60, 26-35.

Chin, J., 2000: Control of Communicable Diseases Manual, 17th edn. The American Public Health Association, Washington, DC:.

Chowell, G., C. E. Ammon, N. W. Hengartner and J. M. Hyman, 2006a: Estimation of the reproductive number of the Spanish flu epidemic in Geneva, Switzerland. Vaccine, 24, 6747-6750.

Chowell, G., C. E. Ammon, N. W. Hengartner and J. M. Hyman, 2006b: Transmission dynamics of the great influenza pandemic of 1918 in Geneva, Switzerland: Assessing the effects of hypothetical interventions. J. Theor. Biol., 241, 193-204.

Chowell, G., C. E. Ammon, N. W. Hengartner and J. M. Hyman, 2007a: Estimating the reproduction number from the initial phase of the Spanish flu pandemic waves in Geneva, Switzerland. Math.Biosci. Eng., 4, 457-470.

Chowell, G., L. M. Bettencourt, N. Johnson, W. J. Alonso and C. Viboud, 2008a: The 1918-1919 influenza pandemic in England and Wales: spatial patterns in transmissibility and mortality impact. Proc. R. Soc. Lond. B. Biol. Sci., 275, 501-509.

Chowell, G., M. A. Miller and C. Viboud, 2008b: Seasonal influenza in the United States, France, and Australia: transmission and prospects for control. Epidemiol. Infect., 136, 852-864.

Chowell, G. and H. Nishiura, 2008: Quantifying the transmission potential of pandemic influenza. Phys. Life Rev., 5, 50-77.

Chowell, G., H. Nishiura and L. M. Bettencourt, 2007b: Comparative estimation of the reproduction number for pandemic influenza from daily case notification data. J. R. Soc. Interface, 4, 155-166.

Ciofi degli Atti, M. L., S. Merler, C. Rizzo, M. Ajelli, M. Massari, P. Manfredi, C. Furlanello, G. Scalia Tomba and M. Iannelli, 2008: Mitigation measures for pandemic influenza in Italy: an individual based model considering different scenarios. PLoS One, 3, e1790.

Coburn, B. J., B. G. Wagner and S. Blower, 2009: Modeling influenza epidemics and pandemics: insights into the future of swine flu (H1N1). BMC Med., 7, 30.

Colizza, V., A. Barrat, M. Barthelemy, A. J. Valleron and A. Vespignani, 2007: Modeling the worldwide spread of pandemic influenza: baseline case and containment interventions. PLoS Med., 4, e13-e13.

Colizza, V., A. Vespignani, N. Perra, C. Poletto, B. Goncalves, H. Hu, D. Balcan, D. Paolotti, W. Van den Broeck, M. Tizzoni, P. Bajardi and J. J. Ramasco, 2009a: Estimate of Novel Influenza A/H1N1 cases in Mexico at the early stage of the pandemic with a spatially structured epidemic model. PLoS Curr., 1, RRN1129.

Colizza, V., A. Vespignani, N. Perra, C. Poletto, B. Goncalves, H. Hu, D. Balcan, D. Paolotti, W. Van den Broeck, M. Tizzoni, P. Bajardi and J. J. Ramasco, 2009b: Estimate of Novel Influenza A/H1N1 cases in Mexico at the early stage of the pandemic with a spatially structured epidemic model. PLoS Curr. Influenza, RRN1129.

Cooper, B. S., R. J. Pitman, W. J. Edmunds and N. J. Gay, 2006: Delaying the international spread of pandemic influenza. PLoS Med., 3, e212-e212.

Couch, R. B. and J. A. Kasel, 1983: Immunity to influenza in man. Annu. Rev. Microbiol., 37, 529-549.

Couch, R. B., J. A. Kasel, W. P. Glezen, T. R. Cate, H. R. Six, L. H. Taber, A. L. Frank, S. B. Greenberg, J. M. Zahradnik and W. A. Keitel, 1986: Influenza: its control in persons and populations. J. Infect. Dis., 153, 431-440.

Cowling, B. J., V. J. Fang, S. Riley, J. S. M. Peiris and G. M. Leung, 2009: Estimation of the serial interval of influenza. Epidemiology, 20, 344-347.

Das, T., A. Savachkin and Y. Zhu, 2008: A large-scale simulation model of pandemic influenza outbreaks for development of dynamic mitigation strategies. IIE Transactions, 40, 893-905.

Davey, V. J. and R. J. Glass, 2008: Rescinding community mitigation strategies in an influenza pandemic. Emerg. Infect. Dis., 14, 365-372.

Davey, V. J., R. J. Glass, H. J. Min, W. E. Beyeler and L. M. Glass, 2008: Effective, robust design of community mitigation for pandemic influenza: a systematic examination of proposed US guidance. PLoS One, 3, e2606.

De Serres, G., I. Rouleau, M. E. Hamelin, C. Quach, D. Skowronski, L. Flamand, N. Boulianne, Y. Li, J. Carbonneau, A. Bourgault, M. Couillard, H. Charest and G. Boivin, 2010: Contagious period for pandemic (H1N1) 2009. Emerg. Infect. Dis., 16, 783-788.

Demicheli, V., D. Rivetti, J. J. Deeks and T. O. Jefferson, 2004: Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev, CD001269.

Desrosiers, R., R. Boutin and A. Broes, 2004: Persistence of antibodies after natural infection with swine influenza virus and epidemiology of the infection in a herd previously considered influenza- negative. J. Swine Health Prod., 12, 78–81.

Doyle, A., I. Bonmarin, D. Daniel Lévy-Bruhl2, Y. l. Strat and J. C. Desenclos, 2006: Influenza pandemic preparedness in France: modelling the impact of interventions. J. Epidemiol. Commun. H., 60, 399-404.

Dube, C., C. Ribble, D. Kelton and B. McNab, 2011: Estimating potential epidemic size following introduction of a long-incubation disease in scale-free connected networks of milking-cow movements in Ontario, Canada. Prev. Vet. Med., 99, 102-111.

Dubé, C., C. Ribble, D. Kelton and B. McNab, 2008: Comparing network analysis measures to determine potential epidemic size of highly contagious exotic diseases in fragmented monthly networks of dairy cattle movements in Ontario, Canada. Transbound. Emerg. Dis., 55, 382-392.

Duerr, H. P., S. O. Brockmann, I. Piechotowski, M. Schwehm and M. Eichner, 2007a: Influenza pandemic intervention planning using InfluSim: pharmaceutical and non-pharmaceutical interventions. BMC Infect. Dis., 7, (13 July 2007)-(2013 July 2007).

Duerr, H. P., M. Schwehm, C. C. Leary, S. J. De Vlas and M. Eichner, 2007b: The impact of contact structure on infectious disease control: influenza and antiviral agents. Epidemiol. Infect., 135, 1124-1132.

Eichner, M., M. Schwehm, H. P. Duerr and S. O. Brockmann, 2007: The influenza pandemic preparedness planning tool InfluSim. BMC Infect. Dis., 7, 17.

Elbakidze, L., 2008: Modeling of avian influenza mitigation policies within the backyard segment of the poultry sector. J. Agr. Econ. Res., 33, 195-211.

Epstein, J. M., D. M. Goedecke, F. Yu, R. J. Morris, D. K. Wagener and G. V. Bobashev, 2007: Controlling pandemic flu: the value of international air travel restrictions. PLoS One, 2, e401.

European, C., 2003: The Netherlands: avian influenza.

Feighner, B. H., J. P. Chrétien, S. P. Murphy, J. F. Skora, J. S. Coberly, J. E. Dietz, J. L. Chaffee, M. L. Sikes, M. J. Mabee, B. P. Russell and J. C. Gaydos, 2009: The pandemic influenza policy model: a planning tool for military public health officials. Mil. Med., 174, 557-565.

Ferguson, N. M., D. A. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn and D. S. Burke, 2005: Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature, 437, 209-214.

Ferguson, N. M., D. A. T. Cummings, C. Fraser, J. C. Cajka, P. C. Cooley and D. S. Burke, 2006: Strategies for mitigating an influenza pandemic. Nature, 442, 448-452.

Ferguson, N. M., A. P. Galvani and R. M. Bush, 2003a: Ecological and immunological determinants of influenza evolution. Nature, 422, 428-433.

Ferguson, N. M., S. Mallett, H. Jackson, N. Roberts and P. Ward, 2003b: A population-dynamic model for evaluating the potential spread of drug-resistant influenza virus infections during community-based use of antivirals. J. Antimicrob. Chemother., 51, 977-990.

Fiore, A., D. Shay, K. Broder, J. Iskander, T. Uyeki, G. Mootrey, J. Bresee and N. Cox, 2008: Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR, 57, 1-60.

Fisman, D. N., R. Savage, J. Gubbay, C. Achonu, H. Akwar, D. J. Farrell, N. S. Crowcroft and P. Jackson, 2009: Older age and a reduced likelihood of 2009 H1N1 virus infection. N. Engl. J. Med., 361, 2000-2001.

Flahault, A., S. Deguen and A. J. Valleron, 1994: A mathematical model for the European spread of influenza. Eur. J. Epidemiol., 10, 471-474.

Flahault, A., S. Letrait, P. Blin, S. Hazout, J. Menares and A. J. Valleron, 1988: Modelling the 1985 influenza epidemic in France. Stat. Med., 7, 1147-1155.

Flahault, A., E. Vergu and P. Y. Boelle, 2009: Potential for a global dynamic of Influenza A (H1N1). BMC Infect. Dis., 9, 129.

Flahault, A., E. Vergu, L. Coudeville and R. F. Grais, 2006: Strategies for containing a global influenza pandemic. Vaccine, 24, 6751-6755.

Fock, R., H. Bergmann, H. Bussmann, G. Fell, E. J. Finke, U. Koch, M. Niedrig, M. Peters, K. Riedmann, D. Scholz and A. Wirtz, 2002: Influenza pandemic: preparedness planning in Germany. Euro Surveill., 7, 1-5.

Fox, J. P., C. E. Hall, M. K. Cooney and H. M. Foy, 1982: Influenzavirus infections in Seattle families, 1975-1979. I. Study design, methods and the occurrence of infections by time and age. Am. J. Epidemiol., 116, 212-227.

Fraser, C., 2007: Estimating individual and household reproduction numbers in an emerging epidemic. PLoS One, 2, e758.

Fraser, C., C. A. Donnelly, S. Cauchemez, W. P. Hanage, M. D. Van Kerkhove, T. D. i. Hollingsworth, J. Griffin, R. F. Baggaley, H. E. Jenkins, E. J. Lyons, T. Jombart, W. R. Hinsley, N. C. Grassly, F. Balloux, A. C. Ghani, N. M. Ferguson, A. Rambaut, O. G. Pybus, H. Lopez-Gatell, C. M. Alpuche-Aranda, I. B. Chapela, E. P. Zavala, D. M. E. Guevara, F. Checchi, E. Garcia, S. Hugonnet and C. Roth, 2009: Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings. Science, 324, 1557-1561.

Fu, Y., 2005: Measuring personal networks with daily contacts: A single-item survey question and the contact diary. Soc. Networks, 27, 169–186.

Fu, Y., 2007: Contact diaries: Building archives of actual and comprehensive personal networks. Field Methods, 19, 194-217.

Galbraith, A. W., J. S. Oxford, G. C. Schild and G. I. Watson, 1969: Study of 1-adamantanamine hydrochloride used prophylactically during the Hong Kong influenza epidemic in the family environment. Bull. World Health Organ., 41, 677-682.

Gani, R., H. Hughes, D. Fleming, T. Griffin, J. Medlock and S. Leach, 2005: Potential impact of antiviral drug use during influenza pandemic. Emerg. Infect. Dis., 11, 1355-1362.

Gao, W., A. C. Soloff, X. Lu, A. Montecalvo, D. C. Nguyen, Y. Matsuoka, P. D. Robbins, D. E. Swayne, R. O. Donis, J. M. Katz, S. M. Barratt-Boyes and A. Gambotto, 2006: Protection of mice and poultry from lethal H5N1 avian influenza virus through adenovirus-based immunization. J. Virol., 80, 1959-1964.

Gardam, M., D. Liang, S. M. Moghadas, J. Wu, Q. Zeng and H. Zhu, 2007: The impact of prophylaxis of healthcare workers on influenza pandemic burden. J. R. Soc. Interface, 4, 727-734.

Germann, T. C., K. Kadau, I. M. Longini, Jr. and C. A. Macken, 2006: Mitigation strategies for pandemic influenza in the United States. Proc. Natl. Acad. Sci. U. S. A., 103, 5935-5940.

Glass, K. and B. Barnes, 2007: How much would closing schools reduce transmission during an influenza pandemic? Epidemiology, 18, 623-628.

Glass, L. M. and R. J. Glass, 2008: Social contact networks for the spread of pandemic influenza in children and teenagers. BMC Public Health, 8, 61.

Glass, R. J., L. M. Glass, W. E. Beyeler and H. J. Min, 2006: Targeted Social Distancing Design for Pandemic Influenza. Emerg. Infect. Dis., 12, 1671-1681.

Glezen, W. P., 1996: Emerging infections: pandemic influenza. pp. 64 - 76.

Glezen, W. P. and R. B. Couch, 1997: Influenza viruses. In: A. Evans and R. Kaslow (eds), Viral Infections of Humans: Epidemiology and Control, 4th edn, pp 473-505. , 4th edn edn., pp. 473-505. Plenum Medical Book Company, New York.

Gojovic, M. Z., B. Sander, D. Fisman, M. D. Krahn and C. T. Bauch, 2009: Modelling mitigation strategies for pandemic (H1N1) 2009. Can. Med. Assoc. J., 181, 673-680.

Goodwin, K., C. Viboud and L. Simonsen, 2006: Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine, 24, 1159-1169.

Grais, R. F., J. H. Ellis and G. E. Glass, 2003: Assessing the impact of airline travel on the geographic spread of pandemic influenza. Eur. J. Epidemiol., 18, 1065-1072.

Grais, R. F., J. H. Ellis, A. Kress and G. E. Glass, 2004: Modeling the spread of annual influenza epidemics in the U.S.: the potential role of air travel. Health Care Manag. Sci., 7, 127-134.

Grenfell, B. T. and R. M. Anderson, 1985: The estimation of age-related rates of infection from case notifications and serological data. J. Hyg. (Lond). 95, 419-436.

Gross, P. A., A. W. Hermogenes, H. S. Sacks, J. Lau and R. A. Levandowski, 1995: The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann. Intern. Med., 123, 518-527.

Guberti, V., M. Scremin, L. Busani, L. Bonfanti and C. Terregino, 2007: A simulation model for low-pathogenicity avian influenza viruses in dabbling ducks in Europe. Avian Dis., 51, 275-278.

Gumel, A. B. and S. M. Moghadas, 2003: A qualitative study of a vaccination model with non-linear incidence. Applied Math. Comput., 143, 409-419.

Gumel, A. B., M. Nuño and G. Chowell, 2008: Mathematical assessment of Canada's pandemic influenza preparedness plan. Can. J. Infect. Dis. Med Microbiol.., 19, 185-192.

Haber, M. J., D. K. Shay, X. M. Davis, R. Patel, X. P. Jin, E. Weintraub, E. Orenstein and W. W. Thompson, 2007: Effectiveness of interventions to reduce contact rates during a simulated influenza pandemic. Emerg. Infect. Dis., 13, 581-589.

Halloran, M. E., N. M. Ferguson, S. Eubank, I. M. Longini, Jr., D. A. T. Cummings, B. Lewis, S. Xu, C. Fraser, A. Vullikanti, T. C. Germann, D. Wagener, R. Beckman, K. Kadau, C. Barrett, C. A. Macken, D. S. Burke and P. Cooley, 2008: Modeling targeted layered containment of an influenza pandemic in the United States. Proc. Natl. Acad. Sci. U. S. A., 105, 4639-4644.

Halloran, M. E., F. G. Hayden, Y. Yang, I. M. Longini, Jr. and A. S. Monto, 2007: Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials. Am. J. Epidemiol., 165, 212-221.

Halloran, M. E., I. M. Longini, D. M. Cowart and A. Nizam, 2002: Community interventions and the epidemic prevention potential. Vaccine, 20, 3254-3262.

Halloran, M. E., I. M. Longini, Jr. and C. J. Struchiner, 1999: Design and interpretation of vaccine field studies. Epidemiol. Rev., 21, 73-88.

Hancock, K., V. Veguilla, X. Lu, W. Zhong, E. N. Butler, H. Sun, F. Liu, L. Dong, J. R. DeVos, P. M. Gargiullo, T. L. Brammer, N. J. Cox, T. M. Tumpey and J. M. Katz, 2009: Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. N. Engl. J. Med., 361, 1945-1952.

Hanley, B., 2006: An object simulation model for modeling hypothetical disease epidemics - EpiFlex. Theor. Biol. Med. Model., 3, 32.

Harper, S., K. Fukuda, T. Uyeki, N. Cox and C. Bridges, 2004: Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR, 53, 1-40.

Hartvigsen, G., J. M. Dresch, A. L. Zielinski, A. J. Macula and C. C. Leary, 2007: Network structure, and vaccination strategy and effort interact to affect the dynamics of influenza epidemics. J. Theor. Biol., 246, 205-213.

Hayden, F. G. and F. Y. Aoki, 1999a: Amantadine, rimantadine, and related agents, antiviral agents. In: V. L. Yu, T. C. Merigan and S. L. Barriere (eds), Antimicrobial therapy and vaccines, eds. edn., pp. 1344-1365. Williams and Wilkins, Baltimore, MD. pp 1344-1365.

Hayden, F. G. and F. Y. Aoki, 1999b: In Antimicrobial Therapy and Vaccines, eds. Yu, V., Meigan, T. & Barriere, S. Williams & Wilkins, Baltimore. pp1344-1365.

Hayden, F. G., R. Belshe, C. Villanueva, R. Lanno, C. Hughes, I. Small, R. Dutkowski, P. Ward and J. Carr, 2004: Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J. Infect. Dis., 189, 440-449.

Hayden, F. G., R. Fritz, M. C. Lobo, W. Alvord, W. Strober and S. E. Straus, 1998: Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. J. Clin. Invest., 101, 643-649.

Hayden, F. G., L. V. Gubareva, A. S. Monto, T. C. Klein, M. J. Elliot, J. M. Hammond, S. J. Sharp and M. J. Ossi, 2000: Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. N. Engl. J. Med., 343, 1282-1289.

Hayward, A. C., R. Harling, S. Wetten, A. M. Johnson, S. Munro, J. Smedley, S. Murad and J. M. Watson, 2006: Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. BMJ, 333, 1241.

Hens, N., G. M. Ayele, N. Goeyvaerts, M. Aerts, J. Mossong, J. W. Edmunds and P. Beutels, 2009: Estimating the impact of school closure on social mixing behaviour and the transmission of close contact infections in eight European countries. BMC Infect. Dis., 9, 187.

Heymann, D., 2004: Control of communicable diseases manual, 18th ed. Washington, DC: American Public Health Association. 700p.

Hinshaw, V. S., R. G. Webster, B. C. Easterday and W. J. Bean, Jr., 1981: Replication of avian influenza A viruses in mammals. Infect. Immun., 34, 354-361.

Hirotsu, N., H. Ikematsu, N. Iwaki, N. Kawai, T. Shigematsu, O. Kunishima and S. Kashiwagi, 2004: Effects of antiviral drugs on viral detection in influenza patients and on the sequential infection to their family members--serial examination by rapid diagnosis (Capilia) and virus culture. Int. Corros. Conf. Ser., 1263, 105-108.

Hollingsworth, T. D., N. M. Ferguson and R. M. Anderson, 2006: Will travel restrictions control the international spread of pandemic influenza? Nat. Med., 12, 497-499.

Howden, K. J., E. J. Brockhoff, F. D. Caya, L. J. McLeod, M. Lavoie, J. D. Ing, J. M. Bystrom, S. Alexandersen, J. M. Pasick, Y. Berhane, M. E. Morrison, J. M. Keenliside, S. Laurendeau and E. B. Rohonczy, 2009: An investigation into human pandemic influenza virus (H1N1) 2009 on an Alberta swine farm. Can. Vet. J., 50, 1153-1161.

Hsu, C.-I. and H.-H. Shih, 2010: Transmission and control of an emerging influenza pandemic in a small-world airline network. Accid. Anal. Prev., 42, 93-100.

Iwami, S., T. Suzuki and Y. Takeuchi, 2009: Paradox of vaccination: is vaccination really effective against avian flu epidemics? PLoS One, 4, e4915.

Iwami, S., Y. Takeuchi and X. Liu, 2007: Avian-human influenza epidemic model. Math. Biosci., 207, 1-25.

Jefferson, T., V. Demicheli, D. Rivetti, M. Jones, C. Di Pietrantonj and A. Rivetti, 2006: Antivirals for influenza in healthy adults: systematic review. Lancet, 367, 303-313.

Jefferson, T., D. Rivetti, A. Rivetti, M. Rudin, C. Di Pietrantonj and V. Demicheli, 2005: Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. Lancet, 366, 1165-1174.

Jones, K. E., N. G. Patel, M. A. Levy, A. Storeygard, D. Balk, J. L. Gittleman and P. Daszak, 2008: Global trends in emerging infectious diseases. Nature, 451, 990-993.

Kawai, N., H. Ikematsu, N. Iwaki, I. Satoh, T. Kawashima, T. Tsuchimoto and S. Kashiwagi, 2003: A prospective, Internet-based study of the effectiveness and safety of influenza vaccination in the 2001-2002 influenza season. Vaccine, 21, 4507-4513.

Kim, K. I., Z. Lin and L. Zhang, 2010: Avian-human influenza epidemic model with diffusion. Nonlinear Anal-Real, 11, 313-322.

Kitching, R. P., M. V. Thrusfield and N. M. Taylor, 2006: Use and abuse of mathematical models: an illustration from the 2001 foot and mouth disease epidemic in the United Kingdom. Rev. Sci. Tech., 25, 293-311.

Kwong, J., T. Stukel, J. Lim, A. McGeer, R. Upshur, H. Johansen, C. Sambell, W. Thompson, D. Thiruchelvam, F. Marra, L. Svenson and D. Manuel, 2008: The effect of universal influenza immunization on mortality and health care use. PLoS Med., 5, e211.

Lange, E., D. Kalthoff, U. Blohm, J. P. Teifke, A. Breithaupt, C. Maresch, E. Starick, S. Fereidouni, B. Hoffmann, T. C. Mettenleiter, M. Beer and T. W. Vahlenkamp, 2009: Pathogenesis and transmission of the novel swine-origin influenza virus A/H1N1 after experimental infection of pigs. J. Gen. Virol., 90, 2119-2123.

Larson, R. C., 2007: Simple Models of Influenza Progression Within a Heterogeneous Population. Oper. Res., 55, 399-412.

Lavenu, A., A. J. Valleron and F. Carrat, 2004: Exploring cross-protection between influenza strains by an epidemiological model. Virus Res., 103, 101-105.

Le Menach, A., E. Vergu, R. F. Grais, D. L. Smith and A. Flahault, 2006: Key strategies for reducing spread of avian influenza among commercial poultry holdings:

lessons for transmission to humans. Proc. R. Soc. Lond. B. Biol. Sci., 273, 2467-2475.

Lee, B. Y., R. R. Bailey, A. E. Wiringa, T. M. Assi and R. H. Beigi, 2009a: Antiviral medications for pregnant women for pandemic and seasonal influenza: an economic computer model. Obstetrics & Gynecology, 114, 971-980.

Lee, B. Y., S. T. Brown, P. Cooley, M. A. Potter, W. D. Wheaton, R. E. Voorhees, S. Stebbins, J. J. Grefenstette, S. M. Zimmer, R. K. Zimmerman, T. M. Assi, R. R. Bailey, D. K. Wagener and D. S. Burke, 2009b: Simulating School Closure Strategies to Mitigate an Influenza Epidemic. J. Public Health Manag. Pract.

Lee, B. Y., S. T. Brown, P. Cooley, M. A. Potter, W. D. Wheaton, R. E. Voorhees, S. Stebbins, J. J. Grefenstette, S. M. Zimmer, R. K. Zimmerman, T. M. Assi, R. R. Bailey, D. K. Wagener and D. S. Burke, 2010: Simulating school closure strategies to mitigate an influenza epidemic. J. Public Health Manag. Pract., 16, 252-261.

Lee, C. W., D. L. Suarez, T. M. Tumpey, H. W. Sung, Y. K. Kwon, Y. J. Lee, J. G. Choi, S. J. Joh, M. C. Kim, E. K. Lee, J. M. Park, X. Lu, J. M. Katz, E. Spackman, D. E. Swayne and J. H. Kim, 2005: Characterization of highly pathogenic H5N1 avian influenza A viruses isolated from South Korea. J. Virol., 79, 3692-3702.

Leroux-Roels, I., A. Borkowski, T. Vanwolleghem, M. Drame, F. Clement, E. Hons, J. M. Devaster and G. Leroux-Roels, 2007: Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial. Lancet, 370, 580-589.

Lessler, J., D. A. Cummings, S. Fishman, A. Vora and D. S. Burke, 2007: Transmissibility of swine flu at Fort Dix, 1976. J. R. Soc. Interface, 4, 755-762.

Lessler, J., N. G. Reich, R. Brookmeyer, T. M. Perl, K. E. Nelson and D. A. T. Cummings, 2009: Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect. Dis., 9, 291-300.

Lipsitch, M., T. Cohen, B. Cooper, J. M. Robins, S. Ma, L. James, G. Gopalakrishna, S. K. Chew, C. C. Tan, M. H. Samore, D. Fisman and M. Murray, 2003: Transmission dynamics and control of severe acute respiratory syndrome. Science, 300, 1966-1970.

Longini, I. M., 1988: A mathematical model for predicting the geographic spread of new infectious agents. Math. Biosci., 90, 367-383.

Longini, I. M., M. E. Halloran, A. Nizam, M. Wolff, P. M. Mendelman, P. E. Fast and R. B. Belshe, 2000: Estimation of the efficacy of live, attenuated influenza vaccine from a two-year, multi-center vaccine trial: implications for influenza epidemic control. Vaccine, 18, 1902-1909.

Longini, I. M., Jr. and M. E. Halloran, 2005: Strategy for distribution of influenza vaccine to high-risk groups and children. Am. J. Epidemiol., 161, 303-306.

Longini, I. M., Jr., M. E. Halloran, A. Nizam and Y. Yang, 2004: Containing pandemic influenza with antiviral agents. Am. J. Epidemiol., 159, 623-633.

Longini, I. M., Jr., J. S. Koopman, M. Haber and G. A. Cotsonis, 1988: Statistical inference for infectious diseases. Risk-specific household and community transmission parameters. Am. J. Epidemiol., 128, 845-859.

Longini, I. M., A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D. A. T. Cummings and M. E. Halloran, 2005: Containing Pandemic Influenza at the Source. Science, 309, 1083-1087.

Longini Jr, I. M., E. Ackerman and L. R. Elveback, 1978: An optimization model for influenza A epidemicsstar, open. Math. Biosci., 38, 141-157

Lunelli, A., A. Pugliese and C. Rizzo, 2009: Epidemic patch models applied to pandemic influenza: contact matrix, stochasticity, robustness of predictions. Math. Biosci., 220, 24-33.

Mannelli, A., L. Busani, M. Toson, S. Bertolini and S. Marangon, 2007: Transmission parameters of highly pathogenic avian influenza (H7N1) among industrial poultry farms in northern Italy in 1999-2000. Prev. Vet. Med., 81, 318-322.

Massad, E., M. N. Burattini, F. A. Coutinho and L. F. Lopez, 2007: The 1918 influenza A epidemic in the city of Sao Paulo, Brazil. Med. Hypotheses, 68, 442-445.

Meat and Livestock Australia, National Livestock Identification System. URL: http://www.mla.com.au/Meat-safety-and-traceability/Livestock-identification (Last accessed on 2 February 2012).

Medlock, J. and L. A. Meyers, 2009: Optimizing allocation for a delayed influenza vaccination campaign. PLoS Curr. Influenza, RRN1134.

Meltzer, M. I., N. J. Cox and K. Fukuda, 1999: The economic impact of pandemic influenza in the United States: priorities for intervention. Emerg. Infect. Dis., 5, 659-671.

Mikolajczyk, R. T., M. K. Akmatov, S. Rastin and M. Kretzschmar, 2008: Social contacts of school children and the transmission of respiratory-spread pathogens. Epidemiol. Infect., 136, 813-822.

Mills, C. E., J. M. Robins and M. Lipsitch, 2004: Transmissibility of 1918 pandemic influenza. Nature, 432, 904-906.

Milne, G., J. Kelso and H. Kelly, 2010: Strategies for mitigating an influenza pandemic with pre-pandemic H5N1 vaccines. J. R. Soc. Interface, 7, 573-586.

Moran, K., S. Maaten, A. Guttmann, D. Northrup and J. Kwong, 2009: Influenza vaccination rates in Ontario children: implications for universal childhood vaccination policy. Vaccine., 27, 2350-2355.

Moser, M. R., T. R. Bender, H. S. Margolis, G. R. Noble, A. P. Kendal and D. G. Ritter, 1979: An outbreak of influenza aboard a commercial airliner. Am. J. Epidemiol., 110, 1-6.

Nicholson, K., 1998: Human Influenza. In Textbook of Influenza, Nicholson KG, Webster RG, Hay AJ (eds). Blackwell Science: London. pp 219–264

Nigmatulina, K. R. and R. C. Larson, 2009: Living with influenza: Impacts of government imposed and voluntarily selected interventions. Euro J. Oper. Res., 195, 613-627.

Nishiura, H., C. Castillo-Chavez, M. Safan and G. Chowell, 2009: Transmission potential of the new influenza A(H1N1) virus and its age-specificity in Japan. Euro Surveill., 14.

Novel Swine-Origin Influenza, A. V. I. T., Dawood FS, Jain S, Finelli L, Shaw MW, L. S, R. Garten, L. Gubareva, X. Xu, C. Bridges and T. Uyeki, 2009: Emergence of a Novel Swine-Origin Influenza A (H1N1) Virus in Humans. N. Engl. J. Med., 360:2605-2615.

Nuño, M., G. Chowell and A. B. Gumel, 2007a: Assessing the role of basic control measures, antivirals and vaccine in curtailing pandemic influenza: scenarios for the US, UK and the Netherlands. J. R. Soc. Interface, 4, 505-521.

Nuño, M., G. Chowell, X. Wang and C. Castillo-Chavez, 2007b: On the role of cross-immunity and vaccines on the survival of less fit flu-strains. Theor. Popul. Biol., 71, 20-29.

Nuño, M., T. A. Reichert, G. Chowell and A. B. Gumel, 2008: Protecting residential care facilities from pandemic influenza. Proc. Natl. Acad. Sci. U. S. A., 105, 10625-10630.

Office International des Epizooties (OIE), 2007: Avian Influenza Technical Disease Cards. Avialable at: http:///www.oie.int/eng/avian_influenza/A_Fiches_IA.pdf (accessed on 15 January 2011). Available at: http:///www.oie.int/eng/avian_influenza/A_Fiches_IA.pdf (accessed January 15 2007).

Ohkusa, Y. and T. Sugawara, 2007: Application of an individual-based model with real data for transportation mode and location to pandemic influenza. J Infect Chemother, 13, 380-389.

Ohkusa, Y. and T. Sugawara, 2009: Simulation model of pandemic influenza in the whole of Japan. Jpn. J. Infect. Dis., 62, 98-106.

OIE, 2007: Avian Influenza Technical Disease Cards. Avialable at: http:///www.oie.int/eng/avian_influenza/A_Fiches_IA.pdf (accessed January 15 2007).

Ortiz-Pelaez, A., D. U. Pfeiffer, R. J. Soares-Magalhaes and F. J. Guitian, 2006: Use of social network analysis to characterize the pattern of animal movements in the initial phases of the 2001 foot and mouth disease (FMD) epidemic in the UK. Prev. Vet. Med., 76, 40-55.

Pasma, T. and T. Joseph, 2010: Pandemic (H1N1) 2009 infection in swine herds, Manitoba, Canada. Emerg. Infect. Dis., 16, 706-708.

Perlroth, D. J., R. J. Glass, V. J. Davey, D. Cannon, A. M. Garber and D. K. Owens, 2010: Health outcomes and costs of community mitigation strategies for an influenza pandemic in the United States. Clin. Infect. Dis., 50, 165-174.

Pourbohloul, B., A. Ahued, B. Davoudi, R. Meza, L. A. Meyers, D. M. Skowronski, I. Villaseñor, F. Galván, P. Cravioto, D. J. D. Earn, J. Dushoff, D. Fisman, W. J. Edmunds, N. Hupert, S. V. Scarpino, J. Trujillo, M. Lutzow, J. Morales, A. Contreras, C. Chávez, D. M. Patrick and R. C. Brunham, 2009: Initial human transmission dynamics of the pandemic (H1N1) 2009 virus in North America. Influenza Other Respi. Viruses, 3, 215-222.

Rao, D. M., A. Chernyakhovsky and V. Rao, 2009: Modeling and analysis of global epidemiology of avian influenza. Environ. Model. & Softw., 24, 124-134.

Rios-Doria, D. and G. Chowell, 2009: Qualitative analysis of the level of cross-protection between epidemic waves of the 1918-1919 influenza pandemic. J. Theor. Biol., 261, 584-592.

Rivetti, D., T. Jefferson, R. Thomas, M. Rudin, A. Rivetti, C. Di Pietrantonj and V. Demicheli, 2006: Vaccines for preventing influenza in the elderly. Cochrane Database Syst. Rev, 3, CD004876.

Rizzo, C., A. Lunelli, A. Pugliese, A. Bella, P. Manfredi, G. S. Tomba, M. Iannelli and M. L. Degli Atti, 2008: Scenarios of diffusion and control of an influenza pandemic in Italy. Epidemiol. Infect., 136, 1650-1657.

Roberts, M. G., M. Baker, L. C. Jennings, G. Sertsou and N. Wilson, 2007: A model for the spread and control of pandemic influenza in an isolated geographical region. J. R. Soc. Interface, 4, 325-330.

Rvachev L and L. J. IM., 1985: A mathematical model for the global spread of influenza. Math. Biosci., 75, 3-22.

Saenz, R. A., H. W. Hethcote and G. C. Gray, 2006: Confined animal feeding operations as amplifiers of influenza. Vector Borne Zoonotic Dis., 6, 338-346.

Sanco, D., 2003: Avian influenza (AI) in the Netherlands, Belgiumand Germany-chronology ofmain events and list of decisions adopted by the commission. Available at: http://europa.eu.int/comm/food/animal/diseases/controlmeasures/avian/chronology_2003_epidemic.pdf (accessed on 15 January 2011).

Sattenspiel, L. and D. A. Herring, 2003: Simulating the effect of quarantine on the spread of the 1918-19 flu in central Canada. Bull. Math. Biol., 65, 1-26.

Savill, N. J., S. G. St Rose, M. J. Keeling and M. E. J. Woolhouse, 2006: Silent spread of H5N1 in vaccinated poultry: a chink in the protection of a caged flock can dramatically increase the chances of a flu outbreak. Nature, 442, 757-757.

Sertsou, G., N. Wilson, M. Baker, P. Nelson and M. G. Roberts, 2006: Key transmission parameters of an institutional outbreak during the 1918 influenza pandemic estimated by mathematical modelling. Theor. Biol. Med. Model., 3, 38.

Shaban, N., M. Andersson, A. Svensson and T. Britton, 2009: Household epidemics: modelling effects of early stage vaccination. Biom.J., 51, 408-419.

Sharkey, K. J., R. G. Bowers, K. L. Morgan, S. E. Robinson and R. M. Christley, 2008: Epidemiological consequences of an incursion of highly pathogenic H5N1 avian influenza into the British poultry flock. Proc. R. Soc. Lond. B. Biol. Sci., 275, 19-28.

Shinde, V., C. B. Bridges, T. M. Uyeki, B. Shu, A. Balish, X. Xu, S. Lindstrom, L. V. Gubareva, V. Deyde, R. J. Garten, M. Harris, S. Gerber, S. Vagasky, F. Smith, N. Pascoe, K. Martin, D. Dufficy, K. Ritger, C. Conover, P. Quinlisk, A. Klimov, J. S. Bresee and L. Finelli, 2009: Triple-Reassortant Swine Influenza A (H1) in Humans in the United States, 2005-2009. N. Engl. J. Med., 360, 2616-2625.

Smith, D. J., 2006: Predictability and preparedness in influenza control. Science, 312, 392-394.

Stegeman, A., A. Bouma, A. R. Elbers, M. C. de Jong, G. Nodelijk, F. de Klerk, G. Koch and M. van Boven, 2004: Avian influenza A virus (H7N7) epidemic in The Netherlands in 2003: course of the epidemic and effectiveness of control measures. J. Infect. Dis., 190, 2088-2095.

Stilianakis, N. I., A. S. Perelson and F. G. Hayden, 1998: Emergence of drug resistance during an influenza epidemic: insights from a mathematical model. J. Infect. Dis., 177, 863-873.

Stiver, G., 2003: The treatment of influenza with antiviral drugs. CMAJ, 168, 49-56.

Stöhr, K., 2004: Influenza. In: Heymann, DL., editor. Control of Communicable Diseases Manual. 18th ed., 18th edn. American Public Health Association; Washington, DC.

Swayne, D. E. and J. R. Beck, 2005: Experimental study to determine if low-pathogenicity and high-pathogenicity avian influenza viruses can be present in chicken breast and thigh meat following intranasal virus inoculation. Avian Dis., 49, 81-85.

Swayne, D. E., C. W. Lee and E. Spackman, 2006: Inactivated North American and European H5N2 avian influenza virus vaccines protect chickens from Asian H5N1 high pathogenicity avian influenza virus. Avian Pathol., 35, 141-146.

Sypsa, V. and A. Hatzakis, 2009: School closure is currently the main strategy to mitigate influenza A(H1N1)v: a modeling study. Euro Surveill., 14, 19240-19240.

Sypsa, V., I. Pavlopoulou and A. Hatzakis, 2009: Use of an inactivated vaccine in mitigating pandemic influenza A(H1N1) spread: a modelling study to assess the impact of vaccination timing and prioritisation strategies. Euro Surveill., 14, 19356-19356.

Tennenbaum, S., 2008: Simple criteria for finding (nearly) optimal vaccination strategies. J. Theor. Biol., 250, 673-683.

Thomas, J. and W. DJ, 2001: Epidemiologic methods for the study of infectious diseases. Oxford University Press.

Tian, G., S. Zhang, Y. Li, Z. Bu, P. Liu, J. Zhou, C. Li, J. Shi, K. Yu and H. Chen, 2005: Protective efficacy in chickens, geese and ducks of an H5N1-inactivated vaccine developed by reverse genetics. Virology, 341, 153-162.

Tiensin, T., M. Nielen, H. Vernooij, T. Songserm, W. Kalpravidh, S. Chotiprasatintara, A. Chaisingh, S. Wongkasemjit, K. Chanachai, W. Thanapongtham, T. Srisuvan and A. Stegeman, 2007: Transmission of the highly pathogenic avian influenza virus H5N1 within flocks during the 2004 epidemic in Thailand. J. Infect. Dis., 196, 1679-1684.

Trapman, P., R. Meester and H. Heesterbeek, 2004: A branching model for the spread of infectious animal diseases in varying environments. J. Math. Biol., 49, 553-576.

Tsai, M. T., T. C. Chern, J. H. Chuang, C. W. Hsueh, H. S. Kuo, C. J. Liau, S. Riley, B. J. Shen, D. W. Wang, C. H. Shen and T. S. Hsu Corresponding Author, 2010: Efficient simulation of the spatial transmission dynamics of influenza. PLoS Curr. Influenza, RRN1141.

Tuite, A., D. N. Fisman, J. C. Kwong and A. Greer, 2009: Seasonal Influenza Vaccine Allocation in the Canadian Population during a Pandemic. PLoS Curr. Influenza, RRN1143.

Tuite, A., D. N. Fisman, J. C. Kwong and A. Greer, 2010a: Optimal pandemic influenza vaccine allocation strategies for the canadian population. PLoS Curr. Influenza, RRN1144.

Tuite, A. R., A. L. Greer, M. Whelan, A. L. Winter, B. Lee, P. Yan, J. Wu, S. Moghadas, D. Buckeridge, B. Pourbohloul and D. N. Fisman, 2010b: Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza. Can. Med. Assoc. J., 182, 131-136.

van den Dool, C., M. J. Bonten, E. Hak, J. C. Heijne and J. Wallinga, 2008: The effects of influenza vaccination of health care workers in nursing homes: insights from a mathematical model. PLoS Med., 5, e200.

van der Goot, J. A., M. C. de Jong, G. Koch and M. Van Boven, 2003: Comparison of the transmission characteristics of low and high pathogenicity avian influenza A virus (H5N2). Epidemiol. Infect., 131, 1003-1013.

van der Goot, J. A., G. Koch, M. C. de Jong and M. van Boven, 2005: Quantification of the effect of vaccination on transmission of avian influenza (H7N7) in chickens. Proc. Natl. Acad. Sci. U. S. A., 102, 18141-18146.

van der Goot, J. A., M. van Boven, G. Koch and M. C. de Jong, 2007: Variable effect of vaccination against highly pathogenic avian influenza (H7N7) virus on disease and transmission in pheasants and teals. Vaccine, 25, 8318-8325.

Vardavas, R., R. Breban and S. Blower, 2007: Can influenza epidemics be prevented by voluntary vaccination? PLoS Comput. Biol., 3, e85.

Vincent, A. L., K. M. Lager, K. S. Faaberg, M. Harland, E. L. Zanella, J. R. Ciacci-Zanella, M. E. Kehrli, Jr., B. H. Janke and A. Klimov, 2010: Experimental inoculation of pigs with pandemic H1N1 2009 virus and HI cross-reactivity with contemporary swine influenza virus antisera. Influenza Other Respi. Viruses, 4, 53-60.

Vincent, A. L., S. L. Swenson, K. M. Lager, P. C. Gauger, C. Loiacono and Y. Zhang, 2009: Characterization of an influenza A virus isolated from pigs during an outbreak of respiratory disease in swine and people during a county fair in the United States. Vet. Microbiol., 137, 51-59.

Vu, T., S. Farish, M. Jenkins and H. Kelly, 2002: A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community. Vaccine, 20, 1831-1836.

Wallinga, J. and M. Lipsitch, 2007: How generation intervals shape the relationship between growth rates and reproductive numbers. Proc. R. Soc. Lond. B. Biol. Sci., 274, 599-604.

Wallinga, J., P. Teunis and M. Kretzschmar, 2006: Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. Am. J. Epidemiol., 164, 936-944.

Ward, M. P., D. Maftei, C. Apostu and A. Suru, 2009: Estimation of the basic reproductive number (R0) for epidemic, highly pathogenic avian influenza subtype H5N1 spread. Epidemiol. Infect., 137, 219-226.

Webster, R. G., R. J. Webby, E. Hoffmann, J. Rodenberg, M. Kumar, H. J. Chu, P. Seiler, S. Krauss and T. Songserm, 2006: The immunogenicity and efficacy against H5N1 challenge of reverse genetics-derived H5N3 influenza vaccine in ducks and chickens. Virology, 351, 303-311.

Wein, L. M. and M. P. Atkinson, 2009: Assessing infection control measures for pandemic influenza. Risk Anal., 29, 949-962.

Welliver, R., A. S. Monto, O. Carewicz, E. Schatteman, M. Hassman, J. Hedrick, H. C. Jackson, L. Huson, P. Ward and J. S. Oxford, 2001: Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. JAMA, 285, 748-754.

Weycker, D., J. Edelsberg, M. Elizabeth Halloran, J. I. M. Longini, A. Nizam, V. Ciuryla and G. Oster, 2005: Population-wide benefits of routine vaccination of children against influenza. Vaccine, 23, 1284-1293.

White, L. F., J. Wallinga, L. Finelli, C. Reed, S. Riley, M. Lipsitch and M. Pagano, 2009: Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA. Influenza Other Respi. Viruses, 3, 267-276.

WHO, 2009: Statement to the press by WHO Director-General Dr Margaret Chan WHO.

Witkop, C. T., M. R. Duffy, E. A. Macias, T. F. Gibbons, J. D. Escobar, K. N. Burwell and K. K. Knight, 2010: Novel Influenza A (H1N1) outbreak at the U.S. Air Force Academy: epidemiology and viral shedding duration. Am. J. Prev. Med., 38, 121-126.

Wood, J. G., N. Zamani, C. R. MacIntyre and N. G. Becker, 2007: Effects of internal border control on spread of pandemic influenza. Emerg. Infect. Dis., 13, 1038-1045.

World Health Organization (WHO), 2009: WHO Statement May 5th (Keiji Fukuda).Available at htpp://whoterrance.vo.msecnd.net/mediacentre/audio/press_briefings/vpc_05MAY2009_Influenza_A_H1N1.mp3.

Wu, J. T., S. Riley, C. Fraser and G. M. Leung, 2006: Reducing the impact of the next influenza pandemic using household-based public health interventions. PLoS Med., 3, e361-e361.

Xu, Y., L. J. S. Allen and A. S. Perelson, 2007: Stochastic model of an influenza epidemic with drug resistance. J. Theor. Biol., 248, 179-193.

Yang Y, Longini IM and H. ME, 2006: Design and evaluation of prophylactic interventions using infectious disease incidence data from close contact groups. J. Roy. Statist. Soc. Ser. C, 55, 317–330.

Yang, Y., I. M. Longini and M. E. Halloran, 2007: A Resampling-Based Test to Detect Person-To-Person Transmission of Infectious Disease. Ann. Appl. Stat., 1, 211-228.

Yang, Y., J. D. Sugimoto, M. E. Halloran, N. E. Basta, D. L. Chao, L. Matrajt, G. Potter, E. Kenah and I. M. Longini, Jr., 2009: The transmissibility and control of Pandemic Influenza A (H1N1) virus. Science, 326, 729-733.

Yasuda, H. and K. Suzuki, 2009: Measures against transmission of pandemic H1N1 influenza in Japan in 2009: simulation model. Euro Surveill., 14, 19385-19385.

Zangwill, K. M. and R. B. Belshe, 2004: Safety and efficacy of trivalent inactivated influenza vaccine in young children: a summary for the new era of routine vaccination. Pediatr. Infect. Dis. J., 23, 189-197.